Tours of High-Containment and Pristine Facilities in Support of Mars Sample Return (MSR) Sample Receiving Facility (SRF) Definition Studies

NASA Tiger Team RAMA

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The decision to implement Mars Sample Return and/or a Sample Receiving Facility will not be finalized until NASA's completion of the National Environmental Policy Act (NEPA) process. This document is being made available for informational purposes only.

This report describes several existing laboratories and those under construction that were visited and studied by the RAMA team to gather valuable lessons for a notional MSR SRF. Descriptions contained in this report do not imply endorsement or promotion. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not constitute or imply its endorsement by the United States Government or the Jet Propulsion Laboratory, California Institute of Technology.

Executive Summary

During 2019 and 2020, the NASA Tiger Team RAMA toured several high-containment biosafety laboratories and pristine space-mission facilities worldwide to better understand their practices, capabilities, and lessons-learned to aid in planning a Sample Receiving Facility (SRF) in support of Mars Sample Return (MSR). The team also included tours of a manufacturer of mobile and modular high-containment facilities as well as manufacturers of isolators and gloveboxes. In addition, the team visited European Space Agency (ESA) facilities already developing a novel double-walled isolator (DWI) and robotic handling techniques in support of an MSR SRF. The RAMA team visits covered several construction modalities for an MSR SRF: (1) a new traditional brick-and-mortar facility; (2) use of an existing brick-and-mortar Biosafety Level 4 (BSL-4) facility; (3) a novel modular BSL-4 approach; and (4) a hybrid combination of brick-and-mortar, modular, and existing facilities.

The RAMA team's observations and findings in this document illustrate that constructing an MSR SRF would combine the complexity of both high-containment and pristine facilities. Although merging negative-pressure biocontainment and positive-pressure cleanroom technology would be challenging, it is achievable. Furthermore, while adopting the Returned Sample Science requirements of the Mars 2020 Mission for contamination control (e.g., reduction of organics and bioburden) is particularly challenging for an MSR SRF, it is feasible with the utilization of novel techniques and technologies. For example, ESA has begun developing a DWI breadboard that may turn out to be a key technology in providing both containment and cleanliness in conjunction with a pristine containment facility.

Depending on the complexity, traditional brick-and-mortar BSL-4 facilities can nominally take a decade or more to design, build, and commission even without unexpected delays. Due to the proposed pressure schemes for the SRF, the RAMA team estimates that an MSR SRF from design to commissioning could take 8 to 12 years depending on construction modality. In order to provide adequate schedule reserve, the RAMA team encourages NASA to start the design definition phase for the potential MSR SRF as soon as possible. Based on the notional MSR campaign schedule for return, construction options may already be time limited, especially if the initial design phases are delayed.

Through these tours and subsequent conversations, the RAMA team discovered that some BSL-4 facilities have experienced significant delays during design, construction, and commissioning (e.g., 5 or more years), which could represent a significant programmatic risk to MSR. Schedule delays have been caused by new requirements levied by regulatory agencies to reduce loss of containment risks, government funding availability/programmatics, poor design/construction practices, the use of inexperienced subcontractors, and poor community engagement. It is critical that NASA begin MSR SRF community engagement as part of site selection and continue through facility design, construction, commissioning, and receiving of samples. In addition, it is equally critical for NASA to begin engagement with regulatory agencies and science stakeholders to set firm requirements before the facility design phase begins.

NASA could leverage an existing BSL-4 facility for at least some SRF activities; however, if anticipated contamination control and science requirements for the facility hold, many of the proposed SRF functions were not deemed feasible in any of the toured BSL-4 facilities. Providing

enough lab space, accepting large equipment, keeping an MSR lab clean, and assuring adequate isolation from other labs so that unsterilized samples could be safely released (pending biohazard assessment) are a few of the challenges. Therefore, in order to utilize any of the toured facilities, MSR science goals and notional contamination control requirements may need to be descoped. Furthermore, given the disparate nature of the proposed biohazard testing for MSR versus traditional terrestrial biohazard testing, techniques and analytical equipment needed for MSR were not available in the labs visited. However, given the potential benefit of leveraging high-containment expertise and infrastructure, existing community buy-in, and possible cost and schedule savings, this option could be further explored once the minimum science requirements are better understood.

Summary thoughts on the facility construction options are highlighted below:

- An MSR SRF new **brick-and-mortar** approach can be tailored to MSR's needs and is the approach used by all U.S. BSL-4 laboratories constructed to date. However, this approach could be the most expensive modality, take the longest to implement, and have significant programmatic risk of delay, as stated above. Given the current MSR campaign timeline to return samples, it is unclear if this option is still viable.
- The utilization of an **existing BSL-4 facility** may be possible depending on the final contamination control and science requirements for the MSR SRF. Due to the internal dimensions of the labs visited and facility structural requirements, it is unlikely that any modification can be made to the facility to meet cleanliness requirements, as stated above. Furthermore, due to possible construction delays, possible capacity issues, and cross contamination vectors, there may also be significant programmatic risks for sharing an existing facility.
- Another approach is building a contemporary **modular facility**. The modular elements would be installed in a traditional building or shell structure. While this approach has only been used for BSL-3/3Ag facilities, it appears feasible. A modular facility has many advantages over a traditional brick-and-mortar facility with lower costs, shorter design/construction/ commissioning schedule, and flexibility for easier retrofits and future expansion.
- Finally, a **hybrid approach** of **combining** the use of either: (1) a modular facility inside a new brick-and-mortar building or (2) a modular and/or brick-and-mortar BSL-4 annex in conjunction with an existing BSL-4 space should be considered. The advantage of a hybrid approach is that the facility could leverage the strengths of each other's approaches.

Beyond facility construction approaches, the RAMA team investigated technologies for isolating and handling Martian samples. ESA has been studying and developing a DWI breadboard along with other sample-handling technologies. NASA and ESA should collaborate as these technologies are developed in tandem with the SRF design. The research and development investment for clean, remote manipulation and robotics at the start of the facility design phase would be beneficial to MSR.

Herein, this document lays out a summary of the 18 facilities toured, and includes 43 observations, 18 findings, and 22 areas of possible follow-up that the RAMA team and others could pursue to enable further findings. The potential scope and challenges of the SRF are highly dependent on the science, contamination control, and planetary protection requirements currently being defined. The RAMA team should have regular interaction with science advisory and regulatory groups to provide feedback and seek answers to questions already posed.

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Introduction

In 2019 and 2020, a small interdisciplinary team at NASA conducted a series of facility visits: Richard Mattingly, JPL; Alvin Smith, JPL; Michael Calaway, Jacobs/JSC; and Andrea Harrington, JSC (referred to as RAMA). The RAMA team has expertise in aerospace engineering, geological sciences, and biological sciences, with specialties in high containment, planetary protection, astromaterials curation, and sample return mission architecture. The mission of the RAMA team was to conduct advanced fact-finding to investigate issues and potential approaches for a notional Mars Sample Return (MSR) Sample Receiving Facility (SRF) for a potential MSR campaign, along with associated infrastructure and equipment. Facility visits were selected from the following categories:

1. **Select high-containment laboratories**,
2. **Pristine space-mission laboratories** where state-of-the-art contamination control was implemented, and
3. **European Space Agency (ESA) technology facilities** where associated equipment testbeds are being studied relevant to an MSR SRF.

The MSR SRF would receive samples from Mars, which is designated by the NASA Planetary Protection Office as the first Restricted Earth Return (RER) mission since the Apollo program ended in 1972. This evokes planetary protection containment of the returned elements at a presumed high-containment Biosafety Level 4 (BSL-4) while maintaining strict contamination control for both sample safety assessment and world-class science. Samples would be studied in high containment, until demonstrated to be safe to release, either by sample analysis or by sterilization.

The report is organized into five (5) sections:

Section 1: High-Containment Facilities

Section 1 reports on visits to select major BSL-4 facilities in the United States, and one in the United Kingdom. The intent was to explore capabilities, approaches, and lessons learned in the development and operations of the facilities. They include facilities at Boston University (BU); Fort Detrick, MD; University of Texas Medical Branch (UTMB), Galveston; Georgia State University (GSU); Kansas State University (KSU); Centers for Disease Control and Prevention (CDC), Atlanta; and Porton Down, United Kingdom (UK).

GSU and Porton Down both use sealed glovebox lines that are rated as Class III Biosafety Cabinets (BSC-III), the equivalent to BSL-4 room containment, which is the primary isolation method anticipated for the MSR SRF.

In addition, the team visited Germfree who designs and manufactures mobile and modular laboratory facilities and toured an operational BSL-3+ modular facility Germfree installed in Singapore.

Section 2: Pristine Facilities

Section 2 reports on facilities dealing with state-of-the-art space-mission cleanliness, contamination control, and pristine sample handling and storage. Ultraclean techniques were observed in visits to the Japan Aerospace Exploration Agency's (JAXA) receiving and curation facility for Hayabusa and Hayabusa2 sample return missions and the payload assembly of ESA's ExoMars rover at Thales Alenia Space, Italy (TAS-I) and Airbus, UK. TAS-I conducted ExoMars payload hardware precision cleaning and assembly inside an ultraclean glovebox cabinet line situated inside a cleanroom facility. The ExoMars rover was assembled in an ultraclean low bioburden stainless steel cleanroom facility at Airbus, UK. The team was also able to visit Comecer, the company that designed and manufactured the Thales Alenia Space cabinet line. Finally, as baselines, the team visited the NASA Astromaterials Acquisition and Curation Office facilities at JSC and Mars 2020 rover assembly, test, and launch operations (ATLO) facilities at JPL. However, these baseline facilities are not the subjects of this report.

Section 3: ESA Technology Facilities

ESA is engaged in technology development for sample processing for MSR in the UK. The team met with the Thales Alenia Space, UK (TAS-UK) remote manipulation (RM) task in association with University of Bristol's Robotics Lab and TAS-UK/University of Leicester double-walled isolator (DWI) task; both have breadboard facilities that were visited. Both technologies are potentially integral parts of an SRF.

Section 4: Summary Observations and Recommended Follow-up

This section summarizes the team's observations and issues that should be followed up upon before further findings can be realized.

Section 5: Findings

The final section of the report contains the team's findings. Most of the recommended follow-up tasks identified in Section 4 are designed to clarify and solidify these findings to support initial requirements definition, trade studies, and development of a path forward to initiate an MSR SRF project.

Acronyms

(if used more than once)

ABSL	Animal Biosafety Level
ACDP	Advisory Committee on Dangerous Pathogens
AIHP	Activated Ionized Hydrogen Peroxide
AIT	Assembly, Integration, and Test
AMC	Airborne Molecular Contamination
APHIS	Animal and Plant Health Inspection Service
APR	Air Pressure Resistant (doors)
ARS	Agricultural Research Service
ATD/GC/MS	Automated Thermal Desorber / Gas Chromatograph / Mass Spectrometer
BCF	Bio-Clean Facility
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSAT	Biological Select Agents and Toxins
BSC-III	Biological Safety Cabinet (BSC) Class III
BSL-3Ag	Biosafety Level 3 (Agriculture)
BSL-3E	Biosafety Level 3 (Enhanced)
BSL-4	Biosafety Level 4
BU	Boston University
CAMR	Centre for Applied Microbiology & Research
CBEID	Center for Biodefense and Emerging Infectious Diseases
CC	Clean Chambers (JAXA)
CDC	Centers for Disease Control and Prevention
CFM	Cubic Feet per Minute
CFRP	Carbon Fiber–Reinforced Polymer
CL3	Containment Level 3 (equivalent of BSL-3 in UK)
COSHH	Control of Substances Hazardous to Health (Regulations)
COTS	Commercial, Off-the-Shelf
CSM	Chlorosulfonated Polyethylene (CSPE) synthetic rubber (or Hypalon)
CT	Computerized Tomography (scanner)
DHMR	Dry Heat Microbial Reduction
DHS	Department of Homeland Security
DRDC	Defense Research and Development Canada
Duke-NUS	Duke University and the National University of Singapore

DWI	Double-Walled Isolator
EDS	Effluent Decontamination System
EEV	Earth Entry Vehicle
EIS	Environmental Impact Statement
EPDM	Ethylene Propylene Diene Monomer (a synthetic rubber)
EPMA	Electron Probe Micro-Analyzer
ESCuC	Extraterrestrial Sample Curation Center (JAXA)
FEIR	Final Environmental Impact Report
FTIR	Fourier-Transform Infrared Spectrometer
GN_2	Gaseous Nitrogen
GNL	Galveston National Laboratory
GSE	Ground Support Equipment
HCL	High-Containment Laboratory
HCC	High-Containment Core (GSU)
HCCL	High-Containment Continuity Laboratory (CDC)
HEPA	High-Efficiency Particulate Air (filter)
HHS	Health and Human Services
HPA	Health Protection Agency
HSE	Health and Safety Executive
HVAC	Heating, Ventilation, and Air Conditioning
IPA	Isopropyl Alcohol
ISAS	Institute of Space and Astronautical Science (JAXA)
ISO	International Organization for Standardization
JAXA	Japanese Aerospace Exploration Agency
KSU	Kansas State University
MEPA	Massachusetts Environmental Policy Act
MMX	Martian Moons eXploration (JAXA)
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometer
MSL	Mass Spectrometry Leak (test)
MSPG	MSR Science Planning Group
NAA	Neutron Activation Analysis
NBAF	National Bio and Agro-Defense Facility
NBTC	National Biocontainment Training Center
NCRR	National Center for Research Resources (under NIH)
NEIDL	National Emerging Infectious Disease Laboratory

NEPA	National Environmental Policy Act
NIAID	National Institute of Allergy and Infectious Diseases
NIBC	National Interagency Biodefense Campus
NIH	National Institutes of Health
NRC	National Research Council
Pa	Pascal
PAPR	Powered Air-Purifying Respirator
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency of Canada
PHE	Public Health England
PIADCNY	Plum Island Animal Disease Center of New York
PMSCF	Planetary Material Sample Curation Facility (JAXA)
POC	Point of Contact
PP	Planetary Protection
PPE	Personal Protective Equipment
PPT	Parts per Trillion
PTFE	Polytetrafluoroethylene (Teflon)
RAMA	First initials of the four-member tiger team
RFI	Request for Information
RM	Remote Manipulation
ROS	Robotics Operating System
RTP	Rapid Transfer Port
SIMS	Secondary-Ion Mass Spectrometry
SRF	Sample Receiving Facility
SSAP	Sample Safety Assessment Protocol
SWG	Sterilization Working Group
TAS-I	Thales Alenia Space, Italy
TAS-UK	Thales Alenia Space, UK (United Kingdom)
TD-GC-MS	Thermal Desorption–Gas Chromatography–Mass Spectrometer
TEM/SEM	Transmission Electron Microscope / Scanning Electron Microscope
TMAH	Tetramethylammonium Hydroxide
ToF-SIMS	Time-of-Flight Secondary-Ion Mass Spectrometer
UK	United Kingdom
ULPA	Ultra-Low Particulate Air (filter)
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USDA	U.S. Department of Agriculture

UTMB	University of Texas Medical Branch
VHP	Vapor-Phase Hydrogen Peroxide
VOC	Volatile Organic Compound
XCT/XRD	X-ray Computed Tomography / X-ray Diffraction

1 High-Containment Facilities

1.1 National Emerging Infectious Diseases Laboratories (NEIDL) at Boston University: Boston, MA

Reason and Justification for Visit

Located in Boston, Massachusetts, the NEIDL is one of the newest BSL-4 laboratories in the country. Since it was not yet at capacity, we were able to tour their laboratories and all the support facilities. At the time of the visit, the laboratory had recently been fully commissioned after initial delays due to a lack of engagement with the South End community. Understanding the lessons learned from construction and community engagement would be vital for MSR.

Facility Description

In 2003, NEIDL was selected by the National Institute of Allergy and Infectious Disease (NIAID) to be one of two national laboratories with BSL-4 capabilities located on a U.S. university campus (University of Texas Medical Branch's Galveston National Laboratory being the other). At the end of 2017, Boston Public Health Commission gave final approval for the NEIDL, operated by Boston University, to become fully operational (Figure 1.1-1). As part of a national network of secure facilities studying infectious diseases, NEIDL is dedicated to the development of diagnostics, vaccines, and treatments to combat infectious disease.

Figure 1.1-1. The NEIDL is located in the heart of Boston University Medical Center near downtown Boston. *[Source: https://www.bumc.bu.edu/surgery/files/2012/04/Vanderwarker_aerial-5x7.jpg]*

The NEIDL is a seven-story, 192,000 ft^2 structure housing more than 70,000 ft^2 of containment laboratory space, of which 30,000 ft^2 is BSL-4 (based on the 2013 National Environmental Policy Act [NEPA] report). Designed to maximize research capacity, only 48% of the space is allocated for administrative and building support. The containment areas have an array of capabilities, including imaging, aerobiology, and other specialized cores and support spaces. The animal research space is designed to accommodate rodents and nonhuman primates, although it is not anticipated that these spaces would be needed for an MSR SRF. The facility also houses a state-of-the-art BSL-4 training simulator to provide hands-on training for research staff, faculty, and some support personnel.

Figure 1.1-2. Exterior view of Boston NEIDL. *[Source: NEIDL]*

The facility is powered from two different substations and has redundant generators with fuel to run for three days, which is enough time to safe the facility.

Containment Methods

NEIDL is a traditional brick-and-mortar facility made from single-pour concrete, coated with multiple layers of epoxy on the floor, walls, and ceilings. The containment lab windows are thick laminated glass that can withstand large differential pressures, since regular glass thicknesses are prone to flex overtime allowing the seals/glazing to leak. As with all high-containment facilities, the BSL-4 laboratory is separately engineered from the rest of the building. This separation is for both decontamination purposes and earthquake protection. Specifically, the BSL-4 laboratory is a separate concrete building poured inside the NEIDL, and it sits above the bedrock, on which the overall facility itself is imbedded. This separation allows the two structures to resonate at different frequencies in case of an earthquake, and a spacer between the buildings

allows for flexibility of movement. Since the laboratory is located within a seismic zone with a moderate-probability hazard of horizontal shaking, this will help protect both the laboratory and the community at large.

NEIDL uses automated hydraulic gaskets on their BSL-4 doors. The entryways are flush with the ground allowing for more ease of access and personnel flow between rooms (Figure 1.1-3).

Figure 1.1-3. BSL-4 laboratories in NEIDL. *[Source: NEIDL]*

While most of the BSL-4 laboratory suites utilize specialized suits to isolate the personnel from biological hazards, NEIDL does have one BSC-III cabinet line (~6' long by 3' wide) within the BSL-4 laboratory. This line is directly attached to a suit lab, which is the nominal point of material transfer. It also has a BSC-III cart for transferring animals. The cabinet lab also had its own gowning and shower room to allow for greater isolation from the rest of the BSL-4 laboratory suite.

Two different types of high-containment suits are used within the BSL-4 laboratories at NEIDL: Honeywell BSL-4 and ILC Dover Chemturion (Figure 1.1-4). Both suits must be hooked up to the house air system (blue or red tubing pictured below). When working in BSL-3 laboratories or within the BSC-III cabinet line, less stringent Tyvek personal protective equipment (PPE) with a powered air-purifying respirator (PAPR) can be donned.

Figure 1.1-4. BSL-4 laboratories in NEIDL. *[Source: NEIDL]*

This facility has BSL-2 and BSL-3 labs integrated, since they are needed to support the BSL-4 labs.

Cleaning and Sterilization Techniques

The techniques utilized for cleaning and sterilization are standard for BSL-4 laboratories built in the same era. For anything (including personnel) to be removed from the laboratory, it needs to go through one of two possible pathways. For non-electronic decontamination and some waste disposal, material must be autoclaved before moving on to either an incinerator or cage washer. For equipment, a treatment of vapor-phase hydrogen peroxide (VHP) or formaldehyde is required. Biosafety cabinets are also sterilized with either VHP or formaldehyde. Personnel with suits on have to go through a 3-minute chemical disinfection shower and then a 4-minute rinse. Dunk tanks and chemical spray are also used.

Although not currently used, chlorine dioxide gas may be implemented in the future since it penetrates well. Facility personnel referenced a study that evaluated chlorine dioxide's effect on electronics, exposing 30 laptops over years with no failures. Chlorine dioxide gas is also quicker than VHP, taking 30 hours to decontaminate a room compared to seven days.

Directly above the lab, high-efficiency particulate air (HEPA) filters are in place to filter air going into and out of the laboratories (Figure 1.1-5, top). The labs are at negative pressure compared to the outside environment. The intake HEPA filters ensure no pathogens are released in case the pressure goes positive in the suite. In order to change out the filters, the air handler is segregated from the laboratory and VHP is used to sterilize the filters before they are removed and replaced.

Below the lab, a three effluent tank decontamination system sterilizes all liquid waste (Figure 1.1-5, bottom). This redundant system is designed for one tank to be filled at a time, with one ready to be filled, and the third acting as backup. The effluent decontamination system runs essentially like an autoclave. Each tank holds 1,500 gallons, and it is anticipated that each tank may reach capacity on a daily or weekly basis, depending on laboratory use. The BSL-4 facility is designed to accommodate up to 50 scientists at a time; however, once at full operational capacity, it is anticipated to accommodate an average of 30–35 scientists.

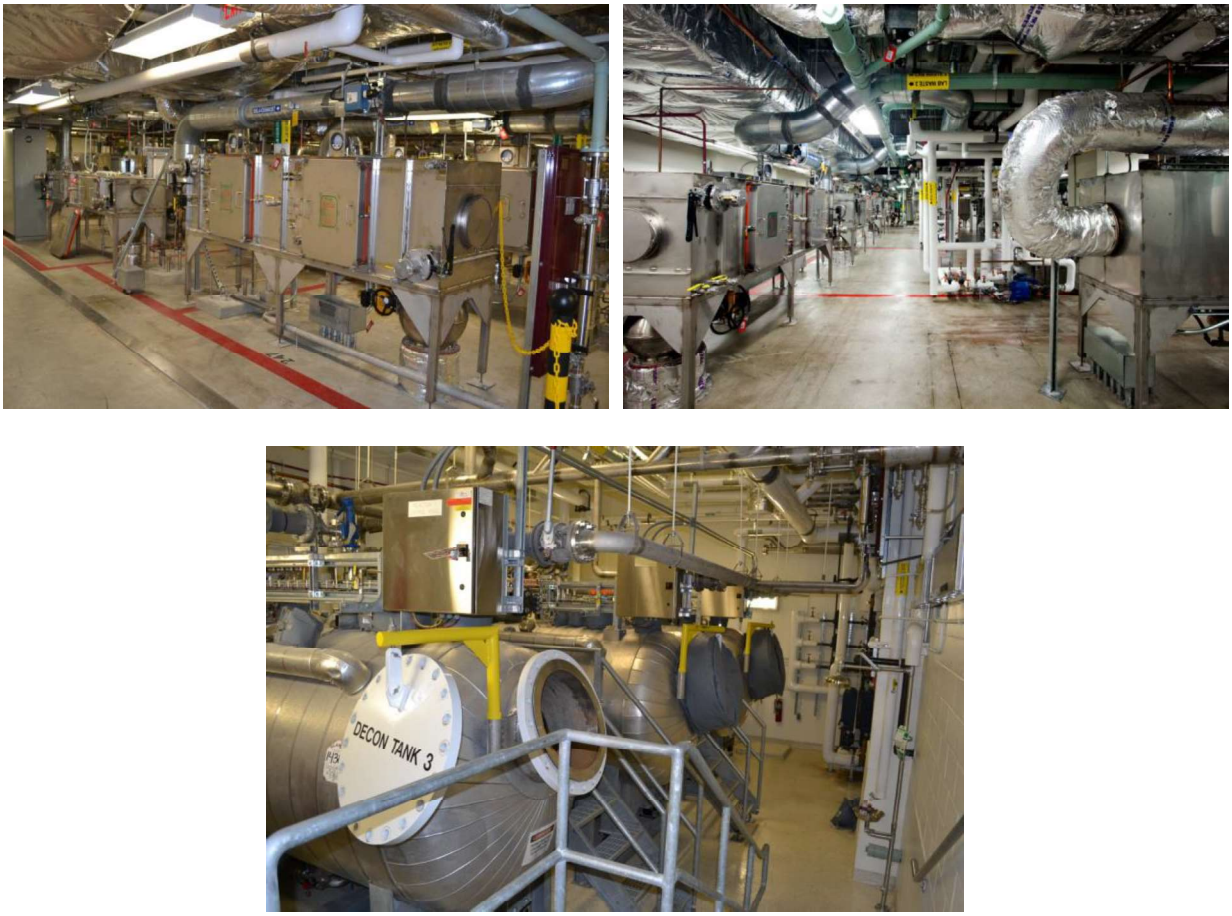

Figure 1.1-5. Infrastructure for cleaning and sterilizing laboratory exhaust and waste. HEPA exhaust filters (top). Effluent decontamination system (bottom). *[Source: NEIDL]*

Pathogens are segregated within different rooms, with their own filtering systems. This segregation allows individual rooms to be decontaminated without having to shut down the whole facility.

Instrumentation/Robotics/Unique Features

In order to help identify the location of a crack or puncture in "hot pipes" to expedite a fix, every pipe out of BSL-4 (sinks and drains) have two stainless steel layers. The pressure of the internal and external volume of the piping is measured to sense if there is a leak in the line. Although this feature may be present in all new BSL-4 construction, it was worth noting the added redundancy emplaced for safety.

NEIDL is the one of two BSL-4 laboratories within the U.S. to have a functional magnetic resonance imaging (MRI) machine for animal imaging within containment. It has a higher resolution than the other one at the Fort Detrick facility. They also have a portable computerized tomography (CT) scanner and a number of other imaging systems.

NEIDL has not utilized robotics as of yet.

NEIDL also has a dedicated BSL-4 training laboratory to help train researchers who would like to work in this environment. The training suite is situated with a change/shower room and a room for donning a pressurized suit. Once in a pressurized suit, personnel can learn how to go through doorway airlocks and work in a fully outfitted suit in the laboratory. One side of the training lab was constructed with windows that look into a conference room. Students and instructors can watch the training exercise in the conference room to help educate the team during training drills and running contingency procedures.

Lessons Learned

Perhaps the most visible lesson that NEIDL leadership shared is the need to acquire public buy-in for the facility early in the process. Due to delays in the National Environmental Policy Act (NEPA) process, the NEIDL was not fully commissioned for BSL-4 work until nearly 2018, almost a decade after construction was complete. Boston University prepared a Final Environmental Impact Report (FEIR) in accordance with the Massachusetts Environmental Policy Act (MEPA), and the National Institutes of Health (NIH) completed their Environmental Impact Statement (EIS) for NEPA around 2003. It is thought that a lack of early community engagement allowed for a perception of secrecy and mistrust and resulted in delays in commissioning of the BSL-4. Although there are other BSL-3 laboratories within the greater Boston area (e.g., Tufts), this is the first one certified for BSL-4 work. Lawsuits were filed in 2005 and 2006, and a judge voided the state's approval of the FEIR because the impact statement failed to consider worst-case scenarios involving accidental or malevolent release of pathogens. Additionally, they did not analyze whether the impact would be materially less if the NEIDL was in a less densely populated area. The NIH published draft comments to these questions, and State of Massachusetts enlisted the help of the National Research Council (NRC) to review the previous risk assessment. The NIH also formed a blue-ribbon panel in 2008 to determine what additional studies were needed to assess potential risks and public health consequences. Final approval (Record of Decision) for NEIDL came from the NIH Office of Research Facilities Development and Operations in 2012. Ultimately, these experiences highlight the need to address the NEPA and other state policies early in the design phase of any facility. It is imperative that the MSR campaign engage with the community to build trust and get their buy-in well in advance; this would be crucial to mission success.

The documents associated with those processes are available in the Resources section. Most notable is the risk assessment report, which provides very extensive assessments for each pathogen they are expecting and concludes with the potential impact of an inadvertent release. These are excellent resources for MSR to understand what is involved in developing their risk assessments.

The NEIDL is only certified to handle known pathogens. Unknown pathogens need to be processed by the CDC (or U.S. Army Medical Research Institute of Infectious Diseases [USAMRIID]) first.

Foreign nationals can have access once they have passed Select Agent background investigation. They have very active collaboration with the UK, countries in Africa, etc.

Training of new personnel requires 100 hours of training and going through 50 lab entries.

The second major lesson learned is regarding construction issues. As is sometimes the case with new construction, the epoxy layer emplaced on the floors, walls, and ceiling of a subset of laboratories began to separate and flake off. Since this epoxy is necessary for biocontainment, it needed to be removed and replaced. This added an additional year to the build.

Cost, Schedule, and Lifespan

In September 2003, NEIDL was chosen as one of two NIAID National Laboratories and in March 2006, construction began. Although construction was completed in the fall of 2008, the facility was not fully commissioned until December 2017. However, BSL-2 and BSL-3 work began in 2012 and 2014, respectively.

NEIDL cost around $197 million dollars to build, of which 75% came from the United States federal government (~$148 million).

Summary

NEIDL demonstrates that the construction of a brick-and-mortar facility may still be an option for MSR. However, delays in commissioning could be an issue if engagement with the local community is not handled properly. Although the length of the design phase is unknown, the sizeable facility was constructed in less than three years (excluding the demolition of any existing facilities). Although it is unlikely that animal models would be used for biohazard assessment within the SRF, the integration of cleanroom technology that would be necessary for MSR means that it is unlikely that this schedule could be shortened.

At the time of writing this report, the BSL-4 laboratory functionality is not at full capacity. The logistics (e.g., space sharing/segregation and infrastructure limitations) of potentially utilizing part of this facility for MSR are unknown.

There is a comprehensive video walkthrough of the facility (see “Treading the NEIDL” in the Resources section). Other resources and fact sheets are also available (see Resources).

Resources

Threading the NEIDL: TWiV Goes Inside a BSL-4. (2013). YouTube: MicrobeWorld; https://www.youtube.com/watch?v=tqAjkjGq8Ug&feature=youtu.be
About NEIDL; https://www.bu.edu/neidl/about-neidl/
NEIDL Resources; https://www.bu.edu/neidl/community/resources/
BU_NEIDL_space_and_facilities_to_NASA_Sept2018.pdf (presentation to NASA)

Links to Risk Assessment and EIS Documents:

http://www.bu.edu/neidl/files/2016/04/**Draft-Supplementary-Risk-Assessment-Readers-Guide-2-12**.pdf

http://www.bu.edu/neidl/files/2010/07/**NEIDL-Final-Environmental-Impact-Statement**.pdf

Final Supplementary Risk Assessment; http://www.bu.edu/neidl/files/2013/01/SFEIR-Volume-III.pdf

http://www.bu.edu/neidl/files/2014/07/**Final-Supplementary-Risk-Assessment-7_2012-Readers-Guide**.pdf

http://www.bu.edu/neidl/files/2010/11/**NRC-Report-on-Continuing-Assistance-to-the-NIH-on-Preparation-of-Additional-Risk-Assessments-for-the-BU-NEIDL-Phase-2**.pdf

Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 3. (2011); http://dels.nas.edu/Report/Continuing-Assistance-National-Institutes/13310

Supplemental Final Environmental Impact Report*;* http://www.bu.edu/neidl/files/2013/01/SFEIR-Volume-I.pdf

NIH Blue Ribbon Panel to Advise on the Risk Assessment of the BU National Emerging Infectious Diseases Laboratories; https://acd.od.nih.gov/documents/reports/ACDBlueRibbonPanel_122011.pdf

1.2 U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick: Frederick, MD

Reason and Justification for Visit

USAMRIID is one of the world's leading facility for conducting high-containment research using some of the world's deadliest pathogens. To better understand the impact for MSR regarding facility plans, this investigation included a visit of the new facility as well as the older building. The original visit toured the existing facility, and the new facility was visited later in the year when it was available for touring, along with participants of the MSR Science Planning Group (MSPG) workshop.

Facility Description

USAMRIID houses some of the most dangerous and infectious biological agents known in the world today, such as Ebola.

- Current USAMRIID (Building 1425): Built in 1969 and features BSL-4 and BSL-3 labs with animal vivarium space for large and small animals.
- New USAMRIID: To be completed in 2020. Features 10,000 ft^2 of BSL-4 space and 50,000 ft^2 of BSL-3 space. It will house a reference (containment) laboratory space maintained at forensic standards, including a secured area for chain-of-custody during sample in-processing, storage, and distribution, as well as a suit and glovebox training lab.

This new six-story research facility, which is part of the existing National Interagency Biodefense Campus (NIBC) located on the Fort Detrick U.S. Army base, replaces the older building and will contain the largest block of state-of-the-art BSL-3 and BSL-4 laboratory suites in the world. Construction and design features include cast-in-place high-containment concrete work, isolation chambers and airlocks, chemical decontamination showers, and extensive state-of-the-art mechanical/electrical/plumbing (MEP) systems. All the utilities, doors, chemical decontamination showers, airlocks, and windows are fully cast into the concrete walls, requiring intense and exacting pre-placement coordination.

The existing USAMRIID facilities on Area A will be decommissioned and either demolished and/or reused following occupancy of the new USAMRIID facilities. NEPA approval was completed years ago when commissioning the entire Biodefense area at Fort Detrick. Community engagement started early. The final EIS can be found in the Federal Register (see Resources section). A video detailing the new facility can be found here: https://youtu.be/t8lXUdyJxkU

Containment Methods

- BSL-2 labs
- BSL-3 labs

- BLS-4 suit labs
- Positive-pressure containment suits
  - Honeywell: white ventilated suit for biological environment; welded safety boots
  - ILC Dover: blue ventilated suit for biological environment
- BSC-I, -II, and -III containment
- Negative-pressure laboratories, anterooms, and hallways
- Positive-pressure room for housing severe combined immunodeficiency (SCID) mouse studies

The current USAMRIID building is comprised of three separate buildings merged into one; there are four levels of biological containment, ranging from BSL-1, the lowest, to BSL-4, the highest. BSL-1 is comparable to an open-bench laboratory found in a school classroom in which no special precautions are needed. At BSL-2, USAMRIID employees wear laboratory coats and observe other basic precautions. For BSL-3 work, personnel change into scrub suits before entering the laboratory and take a complete shower before exiting. Other personal protective equipment may be required as well, depending on the tasks to be performed. BSL-4 is the highest level of containment, and employees wear positive-pressure suits colloquially called “space suits” and breathe filtered air as they work. All personnel will be registered in the Biological Reliability Program and undergo suit and laboratory training, which could last several months to a year, depending on the skill level of the staff.

Figure 1.2-1. Exterior of the current USAMRIID built in 1969. *[Source: https://globalbiodefense.com/]*

The new USAMRIID building(s) will be designed, constructed, verified, and operated according to all the design and engineering standards specified by CDC/NIH (2007) and the applicable requirements of the Biological Defense Safety Program set forth in AR 385-69 and DA PAM 385-69. The facility will be credentialed according to the specifications of the CDC Division of Select Agents and Toxins and/or the counterpart regulations of the U.S. Department of

Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS) that apply to Biological Select Agents and Toxins (BSAT).

Figure 1.2-2. Exterior artist concept of the new USAMRIID to be completed in 2020. *[Source: HDR]*

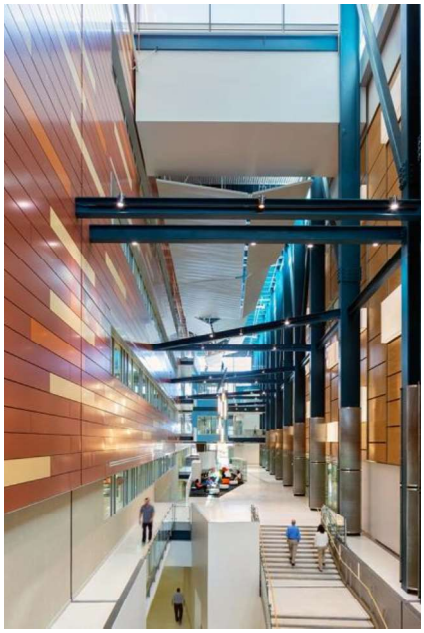

Figure 1.2-3. Interior of the new USAMRIID to be completed in 2020. *[Source: HRD]*

Figure 1.2-4. RAMA team and MSPG members pose with Ft. Detrick leaders during tour in 2019. *[Source: USAMRIID]*

Cleaning and Sterilization Techniques

The facility will have redundant in-line HEPA air filters for air handling. All labs will have the capability to use VHP for decontamination. Chlorine dioxide gas is used in the original USAMRIID. Micro-Chem will also be used for the chemical showers.

Instrumentation/Robotics/Unique Features

The current and new USAMRIID buildings do not use robotics widely. There has been some limited use of high-throughput robotics for sample processing, but these are mostly for repeated processes (e.g., pipetting).

USAMRIID scientists will continue to focus on identification and initial development of medical countermeasures—such as vaccines, drugs, and diagnostics—to protect military personnel against biological threats and naturally occurring endemic diseases.

Lessons Learned

Building high-containment laboratories can be complex and often riddled with delays. These delays could be due to a variety of things, including problems uncovered during environmental compliance processes, building material compatibility, or inspection and regulatory clearance. The building, commissioning, and regulatory approval process could take more than 10 years; therefore, it is advised to properly plan enough margin when projecting timelines for completion.

It was stated that 160 days per year were spent in inspection.

Cost, Schedule, and Lifespan

Estimated costs of the new USAMRIID building started at $650M and ended at $1.1B as of 2020. The average lifespan of a BSL-4 containment building is about 20 years, although the current one built in 1969 is still operational. This building has had several maintenance issues in recent years, which has led to closure by regulatory agencies like the CDC.

The Army began construction on the new building in 2007, which was originally planned to open in 2017. The building is scheduled to be released to the Army in 2020.

Summary

Overall, USAMRIID is a world-renowned facility with expertise that could be leveraged in building and operating the SRF. Additionally, because the new USAMRIID will have more capacity for conducting high-containment research and storage, it may represent an alternative to building a new facility. Unfortunately, both facilities would not meet the stringent cleanliness requirements, even with additional decontamination measures, for the Martian samples. Additionally, because of the low ceiling height of the BSL-4 laboratories in the new facility, modifying a room to include an International Organization for Standardization (ISO) tent or additional HEPA filtration for cleanliness may not be possible. USAMRIID could be ideal for BSL-4 suit training, non-pristine biohazard testing, or long-term storage of sealed samples, if these options are necessary for an SRF or long-term curation in containment.

Resources

https://www.nap.edu/catalog/12871/**evaluation-of-the-health-and-safety-risks-of-the-new-usamriid-high-containment-facilities-at-fort-detrick-maryland**

Video: USAMRIID – The Cornerstone of National Medical Biodefense; https://youtu.be/t8lXUdyJxkU

New USAMRIID Final Environmental Impact Statement 2007; https://www.nrc.gov/docs/ML1004/ML100481112.pdf

1.3 National Bio and Agro-Defense Facility (NBAF) at KSU: Manhattan, KS

Reason and Justification for Visit

NBAF is primed to be the nation's leading facility for agricultural research in animal and zoonotic infections. The facility will be the official replacement for USDA's current high-containment facilities on Plum Island, New York and is poised to be the largest high-containment facility in the country. To better understand the facility planning needs and potential issues for an MSR SRF facility, this trip was planned to visit Department of Homeland Security (DHS) and USDA's new BSL-4 facility at the height of active construction.

Figure 1.3-1. Artist concept of the exterior of NBAF located in Manhattan, KS. *[Source: https://www.k-state.edu/media/newsreleases/mar15/nbafconstruction3615.html]*

Figure 1.3-2. Exterior of NBAF located in Manhattan, KS at about 65% compete in 2018. *[Source: https://www.kansas.com/news/politics-government/article218128635.html]*

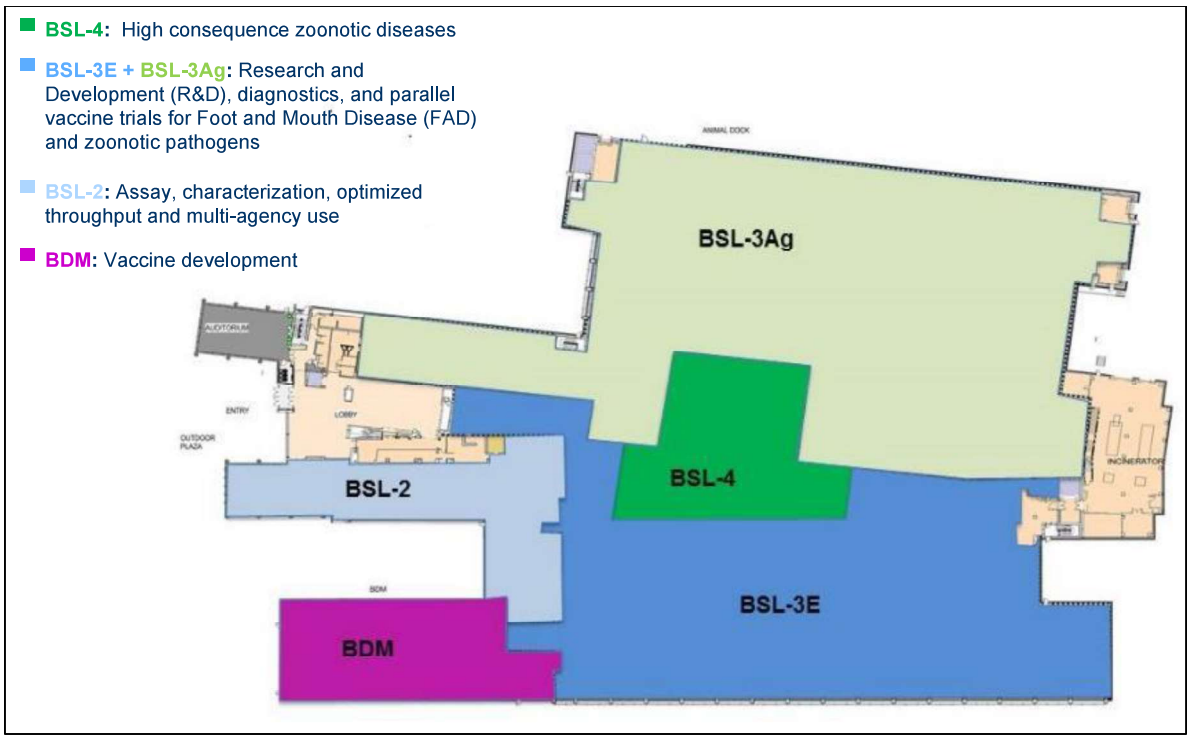

Figure 1.3-3. NBAF laboratory plan (does not include the central utility plant). *[Source: NBAF]*

Facility Description

The USDA is working with the DHS to bring the new NBAF online in Manhattan, Kansas. This state-of-the-art facility will replace the aging high-containment infrastructure and research laboratories at the USDA Plum Island Animal Disease Center of New York (PIADCNY). The DHS Science and Technology Directorate is building the facility to standards that fulfill the mission needs of the USDA, which will own, manage, and operate the NBAF once construction and commissioning activities are complete. USDA's Agricultural Research Service (ARS) and APHIS will conduct foreign animal disease research, training, and diagnostics in the facility.

The NBAF will be the first laboratory facility in the U.S. to provide BSL-4 laboratories capable of housing cattle and other large livestock. The NBAF will also feature a Biologics Development Module for the pilot-scale development of vaccines and other countermeasures, augmenting laboratory research and accelerating technology transfer to industry partners. NBAF modernizes and expands the mission of the highly successful PIADCNY, which has been in operation since 1954.

The NBAF will be constructed and operated on a secure, federally owned site on the northeast corner of the KSU campus, adjacent to KSU's Biosecurity Research Institute in Pat Roberts Hall.

Containment Methods

- BSL-2: 9,700 ft^2
- BSL-3E and BSL-3Ag: 81,000 ft^2
- BSL-4: 13,400 ft^2

To manage the high-consequence pathogens to be studied within NBAF, the facility is designed as a self-contained operation. The completed site will be over 700,000 ft^2. The main laboratory building provides 574,000 ft^2 of integrated laboratory space, animal spaces, support areas, and required safety systems. Other structures total 135,000 ft^2, including the central utility plant, visitor center, transshipping building, and wastewater treatment plant.

BSL-2

The BSL-2 laboratories at NBAF will maintain and provide cell lines cultured for use in the diagnostic and research laboratories. These cell lines provide the necessary substrate for growth of viruses in order to develop methods to quickly diagnose and control the spread of animal diseases. Scientists work in carefully controlled areas to ensure cell lines are maintained clean and pathogen-free prior to use within the containment laboratories.

BSL-3E and BSL-3Ag

The BSL-3E (Enhanced) spaces are the laboratories where assays for disease detection are conducted and developed, and research for discrete identification of the infectious agents, disease epidemiology, and disease origin are conducted. After learning about each virus, vaccines can then be formulated to further protect livestock through vaccination.

The BSL-3Ag (Agriculture) spaces are the prime workspace to understand how animal diseases spread within and among large livestock populations in order to best learn how to diagnose and control the disease within the animals themselves. This space will be used by the APHIS Vaccine Bank to periodically test stockpiled vaccines for efficacy.

BSL-4

NBAF will have the first large-animal BSL-4 capability in the United States. BSL-4 is the highest level of biocontainment and biosafety precautions. This new laboratory capability for USDA will allow disease work to be done with pathogens that could cause severe to fatal disease in commercial livestock and/or humans. For NBAF, the work in this laboratory will involve zoonotic animal diseases or diseases that are transmissible to humans. For this reason, special procedures and equipment (e.g., fully contained suits with dedicated air supply) are necessary to work within this space, and all veterinarians, animal handlers, and scientist must train for months to a year before working in the BSL-4 laboratory. The BSL-4 suite includes BSL-4 laboratory space, Animal

Biosafety Level (ABSL)-4 small-animal space, BSL-4 large-animal space, and necropsy space. For large-animal processing, the ceilings are an impressive ~30 ft in some places.

Cleaning and Sterilization Techniques

The facility has dual redundant inline HEPA air filters for air handling, so that they can be changed out without shutting the room down. Critical facility systems have 100% backup and redundancy. The facility will have access to VHP and chlorine dioxide for decontamination of laboratory areas. VHP is primary, but because it leaves residual water, it is not good for electronics, and it takes about 8 hours for decontamination. Some areas use chlorine dioxide, which only takes 2 hours, but it can be corrosive to stainless steel, requiring air pressure resistant (APR) doors to be replaced periodically.

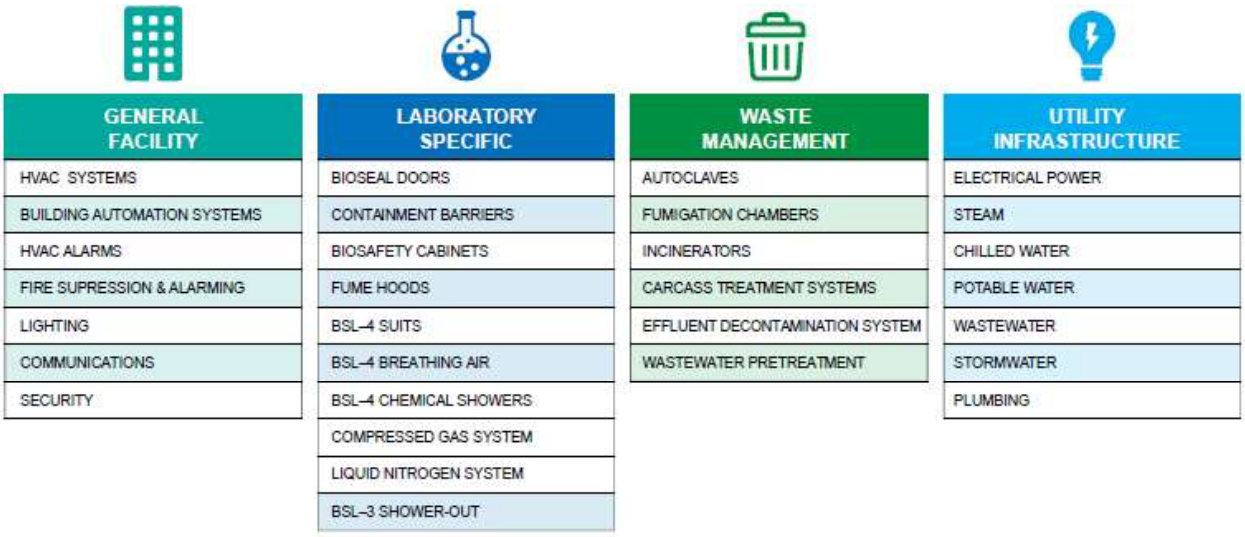

Figure 1.3-4. Critical NBAF systems and associated equipment. *[Source: NBAF]*

Instrumentation/Robotics/Unique Features

NBAF is not planning to use robotics widely. As with many labs working with many samples, the use of high-throughput robotics for sample processing, for repeated processes (e.g., pipetting) could be used.

Lessons Learned

The NEPA process took 1½ years and considered 27 sites. Some states offered to put in funds.

The EIS needed for the NEPA process was very specific for the geographical location of the facility. At the request of Congress, the design team needed to develop a novel testing strategy to demonstrate effectiveness against tornado-strength winds and the barometric pressure differentials that occur during a tornado.

> *The NBAF is designed and "built to withstand wind pressures up to 170% of the winds which are expected to occur locally within a period of 50 years. This means the building's structural system could resist a wind speed that is expected to occur, on the average, only once in a 500-year period. In the unlikely event that a 500-year wind storm strikes the facility, the interior BSL-3Ag and BSL-4 spaces would be expected to withstand a 200 mph wind load (commonly determined to be an F3 tornado)….Since the walls of the BSL-3Ag and BSL-4 spaces would be reinforced cast-in-place concrete, those inner walls would be expected to withstand the tornado." [Source: NBAF FEIS]*

Design changes to mitigate the tornado threat added over $200M to the initial cost of the facility and required incorporation into an existing design that was already under construction. It included ½-inch steel plates to withstand the impact of a 4,000-lb. car at 90 miles per hour. It also had to deal with high pressure differentials (33 in H_2O including a 32% margin). The NBAF team urged the NASA team to start the NEPA process for site selection very early as this could be a driver for addressing any concerns that may come up during the an EIS process. Using the NBAF EIS as a lessons-learned document, the NBAF team offered to share this final document. The final EIS can be found within the Federal Register (see Resources section).

Partnering with a university could be helpful in maintaining a student pipeline of expertise rotating into the building. Given the nature of BSL-4 laboratory researchers to move around to different facilities, there is often high staff turnover, and difficulty maintaining institutional knowledge during transitions.

The original appropriated cost of the facility was $440M. However, due to the rethinking of requirements by multiple agencies and Congress, the facility more than doubled in cost to $1.25B+.

DHS also seemed to have an incredible collaborative interdisciplinary team for design and construction of NBAF. This included:

- McCarthy Mortenson NBAF A Joint Venture
- Perkins+Will
- Flad Architects
- Merrick & Company
- AEI Engineering Inc.
- CCRD Partners

The NBAF management presented elements of their plan and important lessons learned (see Resources); including evidence-based facility engineering, the value of mock-ups (especially for "embed" penetrations through the concrete), and building in the capabilities to adapt to

changing scientific needs. The development of documents to smoothly guide safety assessment teams through their system and processes was emphasized.

Cost, Schedule, and Lifespan

NBAF construction and commissioning will cost $1.25 billion (as of 2019). The $1.25 billion acquisition cost was fully funded in FY15 through a combination of $938 million in federal appropriations, $307 million in funding provided by the State of Kansas, and $5 million from the City of Manhattan (Kansas).

NBAF began construction May 2015 and is scheduled to finish lab construction in December 2020. Full operational capacity is scheduled for December 2022. Annual operating cost of this facility is currently estimated at $100M+/year.

Summary

The NBAF promises to be the world's most advanced lab focusing on the protection of our nation's food supply, agricultural economy, and public health and safety. This will place NBAF at the nexus of the biodefense and agro-defense domains and replace PIADCNY as a leader among biocontainment laboratories.

Overall, the BSL-4 space, while having the proper ceiling height for SRF's double-walled isolators or an ISO tent, will likely not meet the stringent cleanliness requirements for MSR sample handling. The facility handles large animals with lots of waste products, which inherently leaves the facility dirty even with large hoses to wash down animal waste. In addition, the BSL-4 space is not suited for sharing with a NASA mission. The lessons learned regarding the EIS process for NEPA are invaluable.

Resources

NBAF presentation to JPL/JSC
NRC Evaluation of the Updated Site-Specific Risk Assessment for Facility in Manhattan Kansas.
http://www.nap.edu/catalog/13031
https://www.dhs.gov/publication/nbaf-final-environmental-impact-statement
https://www.dhs.gov/xlibrary/assets/nbaf_ssra_final_report.pdf

1.4 Galveston National Laboratory (GNL) at the University of Texas Medical Branch (UTMB): Galveston, TX

Reason and Justification for Visit

GNL is one of two BSL-4 facilities in Galveston, Texas. Due to its proximity to NASA JSC (30 miles southeast), NASA's Astromaterials Acquisition and Curation Office has been in contact with personnel from the laboratory since 2004 as part of MSR planning efforts. Furthermore, while most of the laboratory utilizes pressurized suits for containment, a glovebox line is also operated. Understanding the tradeoffs between these two types of containment facility paradigms and compiling the lessons learned would be vital for designing requirements for an MSR SRF.

Facility Description

Since 2008, GNL has operated under the umbrella of UTMB's Institute for Human Infections and Immunity. One of only two National Laboratories with BSL-4 capabilities located on a U.S. university campus (Boston University's NEIDL being the other), GNL is an anchor lab of the NIAID Biodefense Laboratory Network. The high-security containment research facility serves as a resource in the global fight against infectious disease, studying disease transmission and pathogenesis as well as diagnostics, therapeutics, and vaccines to combat an array of global diseases (e.g., Ebola, Marburg, MERS, Zika, COVID-19). The animal research space is designed to accommodate rodents, nonhuman primates, and avian species. Although the prime funding source is NIAID, research funding also comes from the U.S. Department of Defense, the CDC, and other federal agencies, as well as academic partners, private foundations, and the biopharmaceutical industry.

Before GNL was established, UTMB had a strong background in biomedical research. Since 1994, it has been home to the Institute for Human Infections and Immunity and the World Reference Center for Emerging Viruses and Arboviruses. This collection was housed in biosafety laboratories (BSL-2, BSL-3, and BSL-4) constructed on campus, including the Robert E. Shope BSL-4 laboratory (1997, formally dedicated in 2003), the first BSL-4 laboratory built on a university campus. In 2001, the Sealy Center for Vaccine Development was established and followed by the Center for Biodefense and Emerging Infectious Diseases (CBEID) in 2003.

GNL is an eight-story structure housing more than 80,000 ft^2 of laboratory space and is built to withstand Category 5 hurricanes (Figure 1.4-1). The facility has already been hurricane tested by successfully surviving a direct eye wall wind impact and storm surge from Category 4 Hurricane Ike in 2008 and massive flooding by Hurricane Harvey in 2017. As a testament to the building's design, no interior damage was reported. The facility only sustained minor cosmetic damage to the outside of the building and some basement areas.

Figure 1.4-1. GNL on Galveston Island. *[Source: https://www.utmb.edu/cbeid]*

Figure 1.4-2. Galveston National Laboratory. *[Source: Perkins&Will website]*

In a separate, but adjoining building, there are additional BSL-2 and BSL-3 laboratories that function as part of the GNL. Also attached by an enclosed companionway, and part of the reason why NIAID chose UTMB as the location of its anchor BSL-4 facility, is the Shope BSL-4 laboratory (Figure 1.4-3).

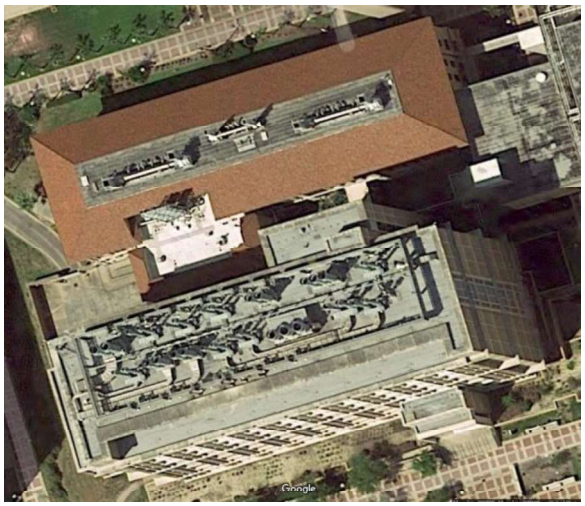

Figure 1.4-3. Aerial view of GNL (bottom) and Shope Laboratory (top; red roof) at UTMB. *[Source:Google Maps]*

Containment Methods

GNL is a traditional brick-and-mortar facility made from single-pour concrete. Structural engineers utilized support pilings driven 120 ft below ground to ensure that all laboratory space is 30 ft above the 100-year floodplain (Figure 1.4-4). The 12,000 ft^2 BSL-4 laboratory is located on the second floor of the building. Other labs located in the building include BSL-2 and BSL-3 facilities that research select and non-select agents in cell cultures, animal, and insects (Kelly, Jim (January 2010) "A Port in the Storm". UTMB Magazine. 10.1: 11–13). Approximately half of the building is dedicated to mechanical space.

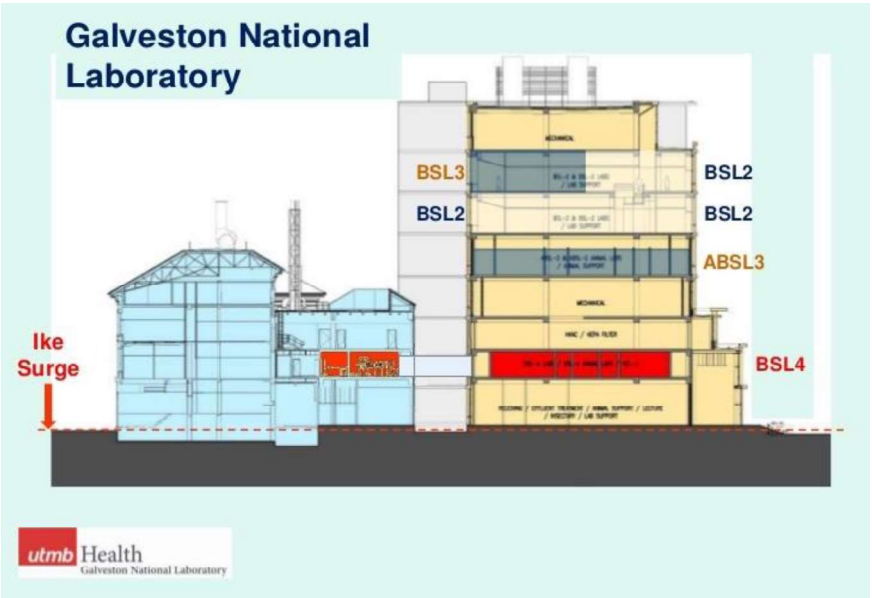

Figure 1.4-4. Profile of GNL at UTMB with containment laboratory locations highlighted. *[Source: UTMB]*

While most of the BSL-4 laboratory suites utilize specialized suits to isolate the personnel from biological hazards, GNL does have one BSC-III cabinet line (~6' long by 3' wide). This line is directly attached to a suit lab, which is the nominal point of material transfer (Figure 1.4-5).

Figure 1.4-5. GNL high containment laboratories.
BSL-4 suite laboratory (left). View into BSL-4 facility (center). BSC-III cabinet (right). *[Source:UTMB]*

There are two different types of suits utilized within the BSL-4 laboratories at GNL: Honeywell BSL-4 and ILC Dover Chemturion (Figure 1.4-6). The white Honeywell suits are made of a thinner material (polyester fabric with polyvinyl chloride [PVC] coating) and are lighter (8–10 lbs.). Due to the material and the integrated HEPA filter, these suits also tend to be easier to manipulate and quieter than the ILC Dover. The blue ILC Dover suits are made of Cloropel (chlorinated polyethylene film) and weigh between 10–18 lbs. Unlike the Honeywell suits, the ILC Dover have external HEPA filtration. Since they are thicker and more resistant to rips and tears, the Dover suits are often preferred when working with animals. Both suits must be hooked up to the house air system (yellow tubing pictured in Figure 1.4-6). For comparison, when working in BSL-3 laboratories or within the BSC-III cabinet line, less stringent Tyvek PPE with a PAPR can be donned.

Figure 1.4-6. High-containment suits. (Continued on next page.)

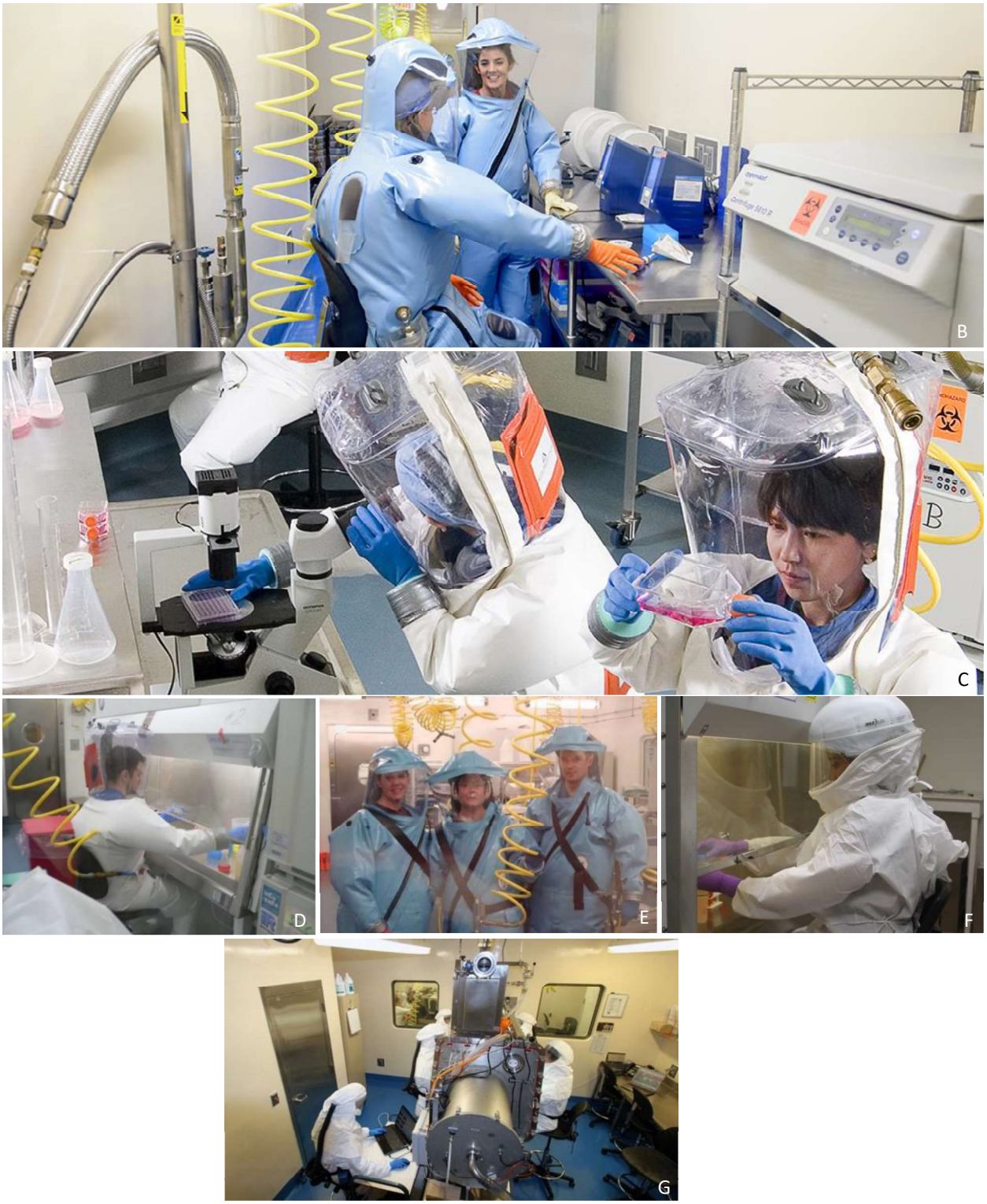

Figure 1.4-6, Continued. Containment suits are shown above: Honeywell white suits (A, C, & D) and ILC Dover blue suits (B & E) for BSL-4. Tyvek PAPR suits for BSL-3 (F & G). Tyvek for BSC-III cabinet (bottom). Image A shows

standard pressure testing and inspection of suits for leaks before donning and entering the BSL-4 space. *[Source: https://www.utmb.edu/gnl/about/about-the-gnl and https://www.utmb.edu/cbeid]*

Cleaning and Sterilization Techniques

The techniques utilized for cleaning and sterilization are standard for BSL-4 laboratories built in the same era. For anything (including personnel) to be removed from the laboratory, it needs to go through one of two possible pathways. For non-electronic decontamination and some waste disposal, material must be autoclaved before moving on to either the incinerator or cage washer. For equipment and suited personal, a treatment of VHP or formaldehyde is required. Biosafety cabinets are also sterilized with either VHP or formaldehyde, with a preference for the former given the deleterious nature of formaldehyde on the equipment and air handling. Directly above the lab, HEPA filters are in place to filter air going into the laboratories and filter air exhaust to capture pathogens before they can be released into the natural environment (Figure 1.4-7; left). Below the lab, an effluent decontamination system sterilizes all liquid waste (Figure 1.4-7; right).

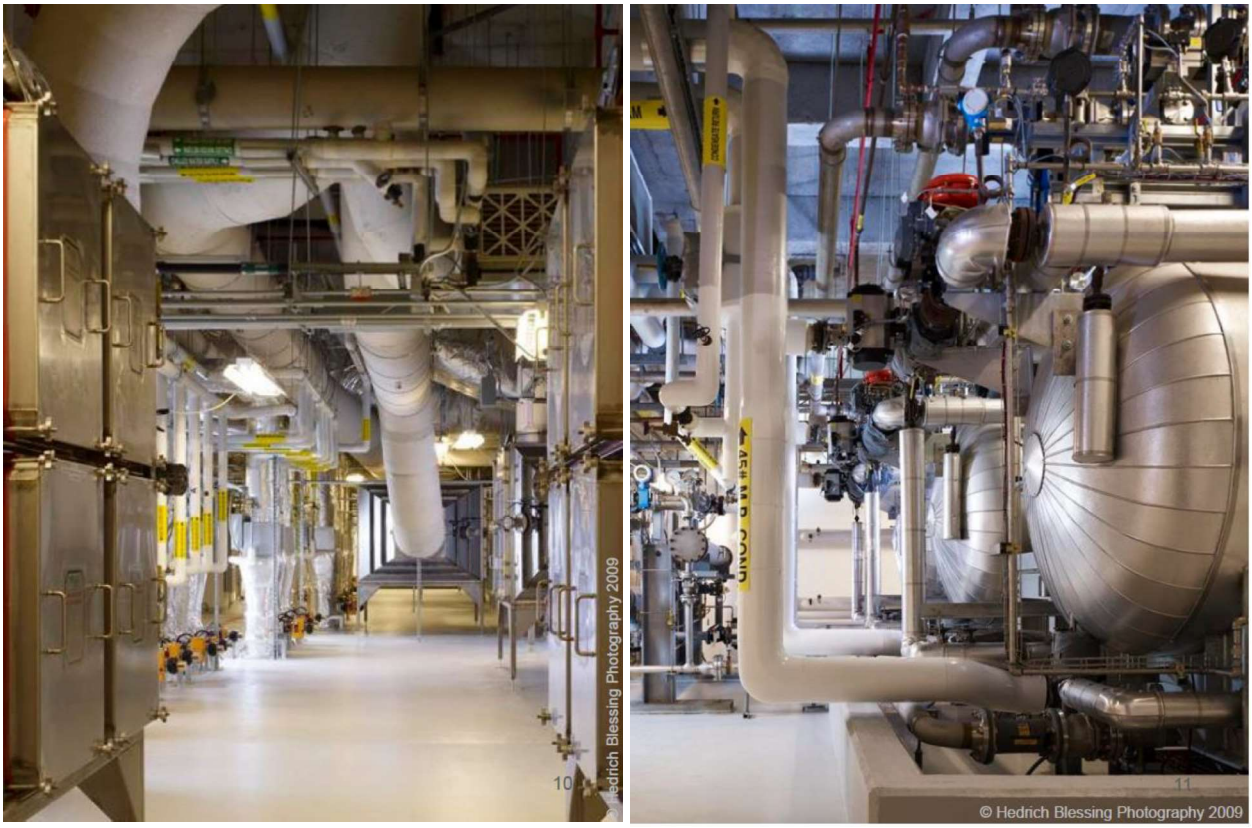

Figure 1.4-7. Infrastructure for cleaning and sterilizing laboratory exhaust and waste. HEPA exhaust filters (left). Effluent decontamination system (right). *[Source:UTMB]*

Instrumentation/Robotics/Unique Features

GNL is outfitted with an array of equipment. The 13+ analytical instruments are distributed throughout its laboratory suites with the bulk being in lower classed laboratories or animal facilities.

However, perhaps the most unique aspect about the laboratory is the push for innovation in both the sterilization systems and biological indicators. Whole room and handheld cold-plasma activated ionized hydrogen peroxide (AIHP) generation systems (SteraMist; Figure 1.4-8) are being evaluated as a replacement for VHP and formaldehyde. It is postulated that AIHP not only distributes throughout the room more affectively (behaving similarly to a gas or plasma instead of vapor) but is also more reactive than VHP and can therefore sterilize an environment more thoroughly and in a less time. The purpose of biological indicator development is to hasten the verification of a room's sterilization. Currently, the protocol relies on culturing techniques, which can take days for verification. However, if successful, the biological indicators could confirm sterilization in a matter of hours (personal correspondence).

Table 1.4-1. GNL Analytical Equipment. *[Source:UTMB]*

Equipment	BSL-2	BSL-3	BSL-4
RuoView 1000 Confocal Microscope	X	X	
Molecular Imager VersaDoc MP 4000 System	X		
Molecular Imager Gel Doc XR System	X		
Personal Molecular Imager (PMI) System	X		
CereTom CT Scanner		X (ABSL)	
microPET Focus 220 PET Scanner		X (ABSL)	
IVIS Imaging System 200 Series		X (ABSL)	X
Point-of-Care CR-ITX Digital X-Ray System		X (ABSL)	
TECAN Freedom EVO	X		
Canto Flow Cytometer			X
TITAN Portable Ultrasound System		X (ABSL)	
InFlux Cell Sorter		X	
Ibis T5000 Universal Biosensor	x		

Figure 1.4-8. SteriMist whole-room AIHP system. *[Source: UTMB]*

It is worth noting that several GNL scientists and facility leads have taken part in both NASA and ESA panels related to MSR and Restricted Earth Returns in the past two decades. Therefore, GNL is familiar with the concept of unknown, unknowns and incorporating contamination control measures into containment facilities. Furthermore, some have led the design and operations of new BSL-4 facilities around the world, including in remote locations.

UTMB also houses the National Biocontainment Training Center (NBTC). Supported through a grant from the U.S. Department of Defense, this is a collaborative effort between the safety professionals of the Environmental Health and Safety Office and the scientists of the GNL. The group offers didactic and practical (mock lab) training to prepare scientists for work with infectious agents (BSL-2 to BSL-4 and ABSL-3).

Lessons Learned

There is a trade-off with the types of isolating doors. While the more automated gaskets in the Shope Laboratory offer an ease of use for daily activities (button activation and doorways flush with floors), when they break, it can require the laboratory to be shut down for an extended period to fix. The manual access doors of GNL require more effort to open/unlock and close/lock (think bank vault) but are more reliable.

Much of the legwork to garner community support was already underway before Galveston was chosen for the NIAID facility due to the efforts to establish the Shope Laboratory. Nevertheless, there are still bimonthly community meetings where university leaders stressed the high-tech safety measures and the economic benefit (Figure 1.4-9) to Galveston (given that 300+ jobs would be created). UTMB also created a permanent advisory committee from residents that

included some critics of the high-containment laboratory. Overall, the campaign was effective, and GNL was constructed with little to no community push-back.

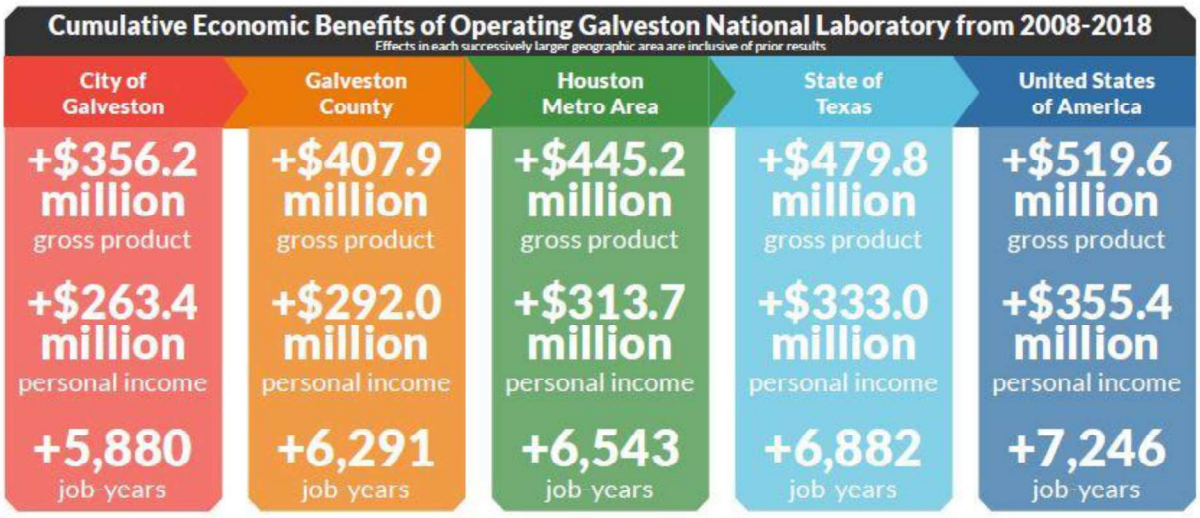

Figure 1.4-9. Summarizing the economic impact of a national laboratory from GNL at UTMB. *[Source: UTMB]*

Cost, Schedule, and Lifespan

GNL was established in 2001 under the direction of U.S. Congress and the NIH. Two year later, after a competitive bidding process, the NIH selected UTMB as the location for one of two of its NIAID laboratories. Before construction could commence, an existing administration building needed to be demolished and existing campus site utilities modified. In 2005 UTMB broke ground for GNL, which officially opened in 2008 and became fully operational two years later in 2010.

GNL cost $173.6 million to build, including $115 million from the federal government (66%) and $58.6 million from the state of Texas.

WSP USA was used as the engineering and commissioning team.

There is no indication as to when GNL would be decommissioned.

Summary

GNL demonstrates that the construction of a brick-and-mortar facility may still be an option for MSR. Although the length of the design phase is unknown, the sizeable facility was constructed in three years and was fully operational within five years of breaking ground (excluding the demolition of existing facilities). Although it is unlikely that complicated animal models would be utilized for biohazard assessment within an SRF, the integration of cleanroom technology necessary for MSR would make it unlikely that this schedule could be shortened. Furthermore, due to its design, it has already withstood major hurricanes and tropical storms with little to no

damage, demonstrating that with proper planning, hurricane zones should not be automatically excluded from consideration for the location of an MSR SRF.

At the time of writing this report, the BSL-4 laboratory functionality seems to be at full capacity. The logistics (e.g., space sharing/segregation and infrastructure limitations) of utilizing part of this facility for MSR are unknown. As with other containment facilities toured, the design of the facility (e.g., ceiling heights, size of access points) may not be able to accommodate the necessary added infrastructure (e.g., isolators, cleanrooms) to meet contamination control standards.

Resources

Kelly, Jim (January 2010). "A Port in the Storm". UTMB Magazine. **10.1**: 11–13.
GNL Home page; https://www.utmb.edu/gnl
Texas State Historical Association article on GNL; https://tshaonline.org/handbook/online/articles/sbgal
Effectiveness of Decontamination of Laboratory Room Surfaces; https://www.mooreasg.com/wp-content/uploads/2017/09/ABSA-AIHP-M.-Grimaldo-Final_2015.V2.pdf
Safety in biocontainment comes with experience; https://www.utmb.edu/impact-archive/archive/article.aspx?IAID=473
https://www.niaid.nih.gov/research/university-texas-national-biocontainment-laboratory
https://www.utmb.edu/gnl/news/2018/12/11/summarizing-the-economic-impact-of-a-national-laboratory
https://www.tmc.edu/news/2014/08/a-solid-foundation-for-biomedical-research/
https://docplayer.net/15480470-Overview-of-the-galveston-national-laboratory.html

1.5 The Shope Laboratory at UTMB: Galveston, TX

Reason and Justification for Visit

Located on the UTMB campus inside the historic Keiller Building and adjacent to the newer GNL, the Robert E. Shope M.D. Laboratory is one of two BSL-4 facilities in Galveston, Texas. Due to its proximity to NASA JSC (30 miles southeast), NASA's Astromaterials Acquisition and Curation Office has been in contact with personnel from the laboratory since 2004 as part of MSR planning efforts. The visit was timed for when the laboratory was down and decontaminated for annual maintenance to enable a tour inside the BSL-4 laboratory itself. Understanding the lessons learned from the construction of Shope and GNL would help optimize the MSR containment facility.

Figure 1.5-1. The historic UTMB Keiller Building that houses the Shope Laboratory in the foreground and the newer GNL in the background. *[Source: https://www.utmb.edu/cbeid]*

Figure 1.5-2. Robert E. Shope M.D. Laboratory, before GNL was built
[Source: UTMB]

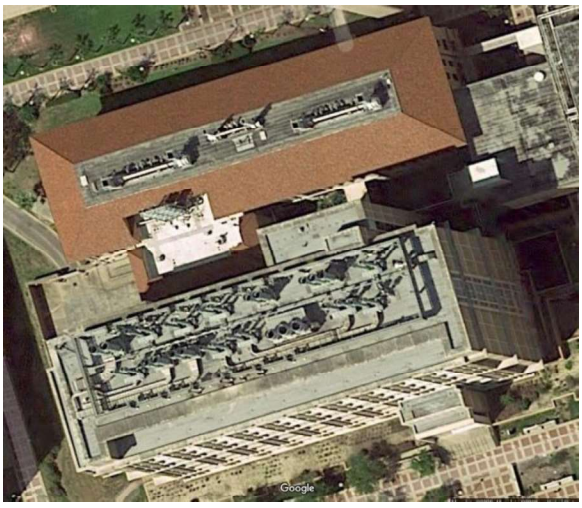

Figure 1.5-3. Aerial view of GNL (bottom) and Shope Laboratory (top, red roof) at UTMB.
[Source: Google Maps]

Facility Description

The Robert E. Shope M.D. Laboratory in the John Sealy Pavilion for Infectious Disease Research (hereafter Shope) is a 12,000 ft^2, high-containment research laboratory attached to GNL. Dedicated in 2003 and operational since 2004, Shope Laboratory is the first full-sized facility of its kind in the nation to be located on a university campus.

UTMB has a strong background in biomedical research. Since 1994, it has been home to the Institute for Human Infections and Immunity and the World Reference Center for Emerging Viruses and Arboviruses. In 1997, UTMB leadership began plans to enable the construction of a BSL-4 laboratory on campus. This was followed by the establishment of Sealy Center for Vaccine Development in 2001 and then the CBEID in 2003.

The Shope Laboratory is an addition inside the existing three-story Keiller Building constructed in 1925, expanded in 1932, and extensive structural renovations in 1995. Due to infrastructure requirements, the BSL-4 laboratory suite is only 2,000 ft^2. The remaining 10,000 ft^2 is required for support equipment. The animal research space is designed to accommodate rodents or smaller animal species. Unlike GNL, the Shope Lab was not specially designed for a Category 5 hurricane since the facility was a retrofit into an existing structure. However, like GNL, the facility successfully survived with no damage from the direct eye wall wind impact and storm surge from Category 4 Hurricane Ike in 2008 and massive flooding by Hurricane Harvey in 2017.

The early success of the Shope Laboratory was a major deciding factor in NIAID's choice of UTMB for the site of their anchor laboratory (GNL)

Containment Methods

Shope Laboratory is a traditional brick-and-mortar facility made from single-pour concrete. The BSL-4 laboratory suite is 30 ft above the 100-year floodplain. The 2,000 ft^2 BSL-4 laboratory suite utilizes specialized suits to isolate personnel from biological hazards (Figure 1.5-4).

Figure 1.5-4. Researchers working in the Robert E. Shope Medical Laboratory at the UTMB. *[Source: UTMB].*

Cleaning and Sterilization Techniques

The techniques utilized for cleaning and sterilization are standard for BSL-4 laboratories built in the same era. For anything (including personnel) to be removed from the laboratory, it needs to go through one of two possible pathways. For non-electronic decontamination and some waste disposal, material must be autoclaved before moving on to either the incinerator or cage washer. For equipment and suited personal, a treatment of VHP or formaldehyde is required. Biosafety cabinets are also sterilized with either VHP or formaldehyde, with a preference for the former given the deleterious nature of formaldehyde on the equipment and air handling system. Directly above the lab, HEPA filters are in place to filter air going into the laboratories and filter air exhaust to capture pathogens before they can be released into the natural environment. Below the lab, an effluent decontamination system sterilizes all liquid waste.

Instrumentation/Robotics/Unique Features

As with GNL, there is an effort to advance current standard sterilization procedures and benchmark biological indicators. Please see the GNL section of this report for more details about these procedures as well as UTMB's National Biocontainment Training Center.

Lessons Learned

Although it was the largest BSL-4 laboratory located on an academic campus at the time, the Shope Laboratory space requirements quickly surpassed the 2,000 ft^2 available. The space insufficiency was due to the amount of proposed work (e.g., wide assortment of pathogens that required investigation) and a design that only accommodated rodent models. Therefore, not only is GNL bigger (the BSL-4 laboratory suite alone is the size of the whole Shope Laboratory facility at 12,000 ft^2) but it is also designed to accommodate an array of animal species, including nonhuman primates.

Due to space limitation, the changing room is small and co-ed. A temporary changing screen is used since the door opens into the hallway. A lighted sign in the hallway can be illuminated to show the occupancy and gender for the changing room.

There is a trade-off with the types of isolating doors. While the more automated gaskets in the Shope Laboratory offer an ease of use for daily activities (button activation and doorways flush with floors), when they break, it can require the laboratory to be shut down for an extended period to fix. The manual access doors of GNL require more effort to open/unlock and close/lock (think bank vault) but are more reliable.

The UTMB leaders began the process of garnering community support early by holding bimonthly community meetings stressing the high-tech safety measures and possible downstream economic benefit to Galveston. UTMB also created a permanent advisory committee from

residents that included some critics of the high-containment laboratory. Overall, the campaign was effective, and the Shope Laboratory was constructed with little to no push-back.

Cost, Schedule, and Lifespan

Construction of the Shope Laboratory began in April 2002 and was completed in 2003. Although operational in 2004, the laboratory was not fully commissioned until 2005. UTMB partnered with the high-containment design firm WPS USA to coordinate the feasibility study. The facility architect was B2HK and the general contractor was Vaughn Construction. Most of the $15.5M construction project was funded by a grant from The Sealy and Smith Foundation of Galveston, a philanthropy solely dedicated to benefiting UTMB, with additional support for the facility from NIH, among other sources.

There is no indication as to when the Shope Laboratory would be decommissioned.

Summary

As with GNL, the Shope Laboratory demonstrates that the construction of a brick-and-mortar facility may still be an option for an MSR SRF. Although the length of the design phase is unknown, the facility was constructed in under two years and was fully operational within three years of breaking ground. Given that it is unlikely that animal models would be utilized for biohazard assessment within the SRF, the commissioning phase could be shortened. However, it is unlikely that construction would be shorter given the small footprint of the laboratory space and the need to integrate cleanroom technology into the SRF. Furthermore, due to its design, it has already withstood major hurricanes and tropical storms with little to no damage, demonstrating that with proper planning, hurricane zones should not be automatically excluded from consideration for the location of an MSR SRF.

Resources

https://www.utmb.edu/cbeid/areas-of-interest/safety-biocontainment
https://www.tmc.edu/news/2014/08/a-solid-foundation-for-biomedical-research/
https://www.utmb.edu/cbeid/areas-of-interest/virology-research
https://www.wsp.com/en-US/projects/university-of-texas-medical-branch-shope-laboratory
Kelly, Jim (January 2010). “A Port in the Storm”. UTMB Magazine. **10.1**: 11–13.
Martin Enserink et al. (2000) Working in the Hot Zone: Galveston’s Microbe Hunters. Science. Vol. 288, Issue 5466, pp. 598-600. DOI: 10.1126/science.288.5466.598

1.6 Centers for Disease Control and Prevention (CDC): Atlanta, GA

Reason and Justification for Visit

The CDC is a U.S. federal agency under the Department of Health and Human Services (HHS) and is the leading national public health institute of the United States. In an effort to better understand the requirements for MSR regarding facility plans, this trip was planned to visit the current BSL-4 facility and discuss the planning for the new facility to be completed in 2025.

Figure 1.6-1. Exterior of CDC High-Containment Lab Building 18.
[Source: https://phil.cdc.gov/Details.aspx?pid=7931]

Facility Description

In 2008, the CDC opened its current High-Containment Laboratory (HCL) Building 18, which holds four BSL-4 suites used to study viral hemorrhagic fevers, smallpox, and highly pathogenic strains of influenza. The CDC is still one of only a handful of facilities in the United States with BSL-4 lab space capable of handling deadly pathogens for which there are no approved treatments or vaccines. Staying abreast of new scientific innovation has allowed the CDC's HCL to play a vital role in investigating and responding to newly discovered infectious diseases. Recognizing the importance of keeping these facilities modern so that CDC can continue its highly specialized work and world-class leadership in laboratory science, Congress approved funding in 2018 to build a new state-of-the-art HCL as current systems begin to age. The new facility is scheduled to be operational in 2025.

Building 18—Current BSL-4 Laboratory

CDC Building 18, the Emerging Infectious Diseases Laboratory, is one of the premier biocontainment facilities of its kind in the world today. Located on CDC's Roybal Campus in Atlanta, Georgia, this 440,000 ft^2 facility is the flagship facility for the HHS in their mission to protect all Americans from infectious disease. Building 18 incorporates BSL-4/3Ag/3/2 laboratories and animal facilities, including specialized research in Q-fever, avian influenza, and other high-consequence agents. The laboratories directly support the CDC Bioterrorism Program, Division of Viral and Rickettsial Diseases, Special Pathogens Branch, Division of AIDS, STD and TB Laboratory Research, and the Division of Bacterial and Mycotic Diseases.

Containment Methods

- BSL-2 labs
- BSL-3 (and 3-Enhanced) labs
- BSL-4 labs

The high-containment area of CDC Building 18 is laid out in four quadrants on the basement level. Each quadrant consists of: 1) a BSL-3E laboratory suite with integrated isolation and centrifuge support areas, associated animal and necropsy rooms, and fumigation room; and 2) a BSL-4 laboratory suite with integrated centrifuge support area, associated animal and necropsy rooms, chemical shower, and fumigation room. The animal rooms are capable of operating in either the BSL-3 or BSL-4 mode to further enhance the flexibility of the laboratory.

The BSL-3 and BSL-4 laboratories are also equipped with dunk tanks, double-door autoclaves, decontamination showers, positive-pressure suits for BSL-4 operations, supply air HEPA filters, and double-HEPA-filtered exhaust air. These components in conjunction with appropriate operating procedures and protocols are in line with Biosafety in Microbiological and Biomedical Laboratories (BMBL) requirements for operation as a BSL-3 or BSL-4 laboratory.

The walls are standard single-pour concrete, coated with epoxy. This construction technique was chosen over stainless steel walls due to cost.

Figure 1.6-2. BSL-2 laboratory space in CDC High-Containment Lab Building 18.
[Source: https://www.mccarthy.com/projects/centers-disease-control]

Figure 1.6-3. BSL-4 laboratory space in CDC High-Containment Lab Building 18.
[Source: https://www.mccarthy.com/projects/centers-disease-control]

Figure 1.6-4. HEPA filter maintenance area at CDC High-Containment Lab Building 18.
[Source: https://www.mccarthy.com/projects/centers-disease-control]

Building 28—New BSL-4 High-Containment Continuity Laboratory (HCCL)

The HCCL will be a highly flexible biological laboratory comprised of BSL-3E and BSL-4 laboratories and associated support (BSL-2 labs). The project is slated to cost $480M. The new multistory research building will house adequate laboratory space for 80 laboratorians but will not currently

feature any new capabilities (i.e., imaging). The HCCL will have a gross building area of approximately 96,000 ft^2. Research space is approximately 16,000 ft^2, and the remaining approximate 80,000 ft^2 supports related mechanical, electrical, and plumbing operations and infrastructure.

All biosafety features and systems of high-containment laboratories will be included, such as HEPA-filtered supply and exhaust air; air pressure resistant doors; effluent collection and treatment; special wall, floor, and ceiling coatings and penetrations; and other systems such as high-purity breathing air and chemical decontamination showers that support BSL-4 workers donning air pressure resistant suits. The epoxy coating on the floors, walls, and ceiling is a hybrid polyurethane that is similar to new epoxy systems that have been used in some recent NASA JSC curation labs.

Ceiling height is about 9–10 feet, which they indicated is typical for BSL-4 facilities. The lab space is about 16% of gross.

Cleaning and Sterilization Techniques

Building 18 has redundant inline HEPA air filters for air handling (Figure 1.6-4). Critical facility systems have 100% backup and redundancy. The facility has access to VHP and chlorine dioxide gas for decontamination and fumigation of laboratory areas. Each laboratory has access to an autoclave for steam sterilization, and some labs may use gamma irradiation to inactivate some laboratory samples. These techniques will also be implemented in Building 28. Biowaste cookers are located in the basement.

Instrumentation/Robotics/Unique Features

The CDC is not currently using or planning to use robotics widely. As with many labs working with many samples, the use of high-throughput robotics for sample processing, for repeated processes (e.g., pipetting) could be used.

One of the old BSL-4 labs that has been set-up to be a training lab and is probably one of the best labs to conduct training drills for alarms and contingency procedures.

The CDC has two sides—one that runs the labs and the other that is a regulatory agency; these functionalities are firewalled from each other.

Lessons Learned

Since the CDC is building the new Building 28 on existing space, a NEPA site selection and traditional EIS is unnecessary. However, the current NEPA statement will need to be updated.

Currently, Building 28 is in the schematic design phase, with the design locked down soon. Also, a bio-repository facility in Lawrenceville, GA (perhaps BSL-3) that is underutilized could be considered for MSR, though this has not been confirmed.

As with NBAF and NEIDL, partnering with a university could be helpful in maintaining a student pipeline of expertise rotating into the building. Many of the CDC researchers have faculty appointments at Emory University. Many students rotate into the CDC laboratories to gain training and expertise. This also helps provide more opportunities for community engagement. Much of the surrounding population is affiliated in some way with the CDC, so it is already sensitized to the ongoing research and potential risks.

Many foreign nationals work at the CDC. Access to the facility requires vetting by the Select Agent program (if needed) and the FBI.

Emory University Hospital has an isolation ward that can be utilized if there are any worker accidents at the CDC (CDC pays them to maintain it). First responders are trained to access the CDC and transport the workers to the Emory isolation ward. This kind of agreement and access to a nearby hospital is needed for any biosafety facility.

Discussions about risk communications were useful and reflected in a detailed trip report.

Although Building 28 provides necessary additional space, the need for the new building was partially based on the inability to retrofit the failing electronic controls in Building 18 because the system was not segmented in a way that allowed replacement without shutting down half of the building for more than a year at a time, which would be too much disruption to CDC operations. A lesson learned is to design systems for ease of retrofit, given accelerating technology advancement. Consideration was given to expanding into the original BSL-4 building, which is used now for training, but it was not deemed to be cost effective to retrofit.

The CDC recommended contacting Case Western National Prion Surveillance Center for information regarding handling and managing prions.

Cost, Schedule, and Lifespan

The new Building 28 will cost an estimated $340M for construction and commissioning ($480M total, which includes upgrades, etc.). It will take about 10 years to build (including a 2-year Project Development Study, a funding authorization period, 1-year procurement process, 1.5-year facility design, 3-year construction, and 2-year certification and commissioning). Started in 2015, it is scheduled to be completed in 2025. It will have an average lifespan of about 20 years, which we were advised is typical.

Summary

The CDC continues to be the nation's leader in public health and advanced high-containment research. As such, they are some of the world's experts in managing and handling biohazards within all levels of containment. The new Building 28 could have the expertise, capacity, and manageable timeline to support anticipated MSR facility needs. Even though the initial design phase is complete, additional discussions and decisions should be made in a timely manner if it

is determined that leveraging this new capacity may be a viable course of action for the SRF. To assess the feasibility of utilizing space to support MSR facility needs, clarifications are necessary to understand the potential of adding additional space and infrastructure to the new Building 28, which is currently finishing up its design phase.

Resources

https://www.mccarthy.com/projects/centers-disease-control
https://phil.cdc.gov/Details.aspx?pid=7931
https://globalbiodefense.com/2018/10/01/cdc-to-build-new-bsl-4-high-containment-continuity-laboratory-hccl/

1.7 Georgia State University (GSU) High Containment Core (HCC): Atlanta, GA

Reason and Justification for Visit

GSU's HCC hosts one of the nation's only glovebox lines for BSL-4 lab experiments. These gloveboxes are rated at BSC-III and are approved for working with pathogens like Ebola and other select agents. In an effort to investigate all technical trades for implementing a high-containment facility for an SRF, it was important to understand GSU's glovebox line as a potential solution for dealing with Martian samples in high-containment.

Facility Description

GSU's HCC, located in Petit Science Center (Figure 1.7-1), is a research facility comprised of BSL-3 and BSL-4 laboratories and animal facilities. It is located in the heart of Atlanta's downtown on the campus of GSU, complete with restaurants for students and the community. Research in the HCC is focused on existing and emerging infectious diseases caused by Ebola virus, Zika virus, West Nile virus, human immunodeficiency virus, herpes B virus, and drug-resistant *Mycobacterium tuberculosis*. It is funded by the NIH, the U.S. Department of Defense, the CDC, and other academic partners and private foundations.

Figure 1.7-1. Petit Science Center, GSU in Atlanta, GA. *[Source: tvsdesign]*

The HCC operates under the collaborative oversight of the researchers and HCC staff. The university's biosafety program is in accordance with federal, state, and local regulations to perform research safely under BSL-2, BSL-3, and BSL-4 maximum-containment laboratory conditions. The Georgia State select agent research program is registered with and regularly inspected by the CDC.

One alternative to the suit room BSL-4 laboratory is the use of BSC-III cabinets as the primary BSL-4 containment barrier. This type of equipment was utilized in many of the early biocontainment facilities (either in an airtight or non-airtight room), but due to the limitations of some of the older cabinet line systems, use of suit laboratory technology has predominated in BSL-4 laboratory design in recent years.

Containment Methods

- BSL-2 labs
- BSL-3 labs
- BSC-I and -II cabinets
- BSL-4 BSC-III cabinet-line
- Negative-pressure laboratories, anterooms, and hallways

BSL-4 Complex

The BSL-4 suite (Figure 1.7-2) is approximately 850 ft^2 and includes a clean dressing room, restroom, shower, PPE dressing room, main lab area, and equipment decontamination/emergency exit. There are three levels of access to the various areas of the BSL-4 complex. The lowest level of access permits entry into BSL-2 areas, with successively higher levels of access provided to the BSL-3 lab and BSL-4 suite. An air pressure gradient is maintained in the BSL-4 complex relative to the exterior areas surrounding the lab. This results in continuous directional negative pressure airflow through non-airtight doors and other exterior areas into more negative pressure lab areas. The greatest negative-pressure differential is maintained in the BSL-4 suite with successively fewer negative pressures present in the BSL-3 lab and the BSL-2 areas. The BSL-3 laboratories remain under negative pressure relative to the laboratory exterior but at a positive pressure balance compared to the BSL-4 suite.

Personnel working in the BSL-2 and BSL-3 labs are provided with a secure changing area to don protective clothing and store personal items in lockers. Lab personnel are required to wear protective scrubs in the BSL-3 lab. Persons entering the BSL-4 suite are required to change into laboratory clothing (red scrubs) worn only in the high-containment areas. Lockers in the clean dressing room store personal items and clothing worn into the dressing area. All personal items such as eyeglasses, jewelry, and watches must be left in the clean dressing area. All materials taken into the main lab area must be decontaminated before removal from the laboratory. A restroom facility is adjacent to the clean dressing room. After changing into protective clothing, passage through a shower area into the PPE dressing area is required to enter the main lab area. A shower is not required during entry into the PPE dressing area, but all persons leaving the PPE dressing area must take a thorough shower.

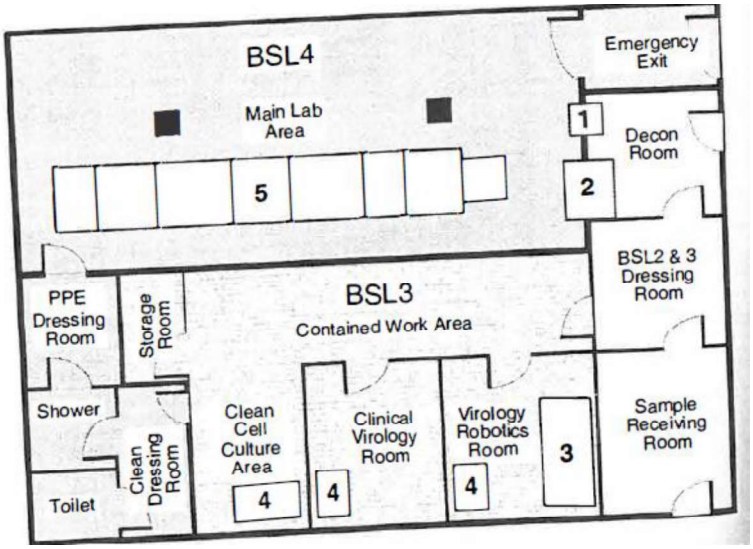

Figure 1.7-2. GSU floor plan for original containment suite. *[Source: Henkel, R.D, et.al.]*

The Class III Cabinet Line

The primary containment barrier in the BSL-4 laboratory is the BSC-III cabinet line. This equipment is used for production of herpes B virus stocks and materials for use in the diagnostic laboratory and for research studies. The original cabinet line was a custom design built by The Baker Company (Sanford, ME) to accommodate the specific needs of the scientists working in the B virus laboratory and to fit into the footprint of the BSL-4 main lab area. There have been several upgrades and replacements made to the cabinet line. Unfortunately, no pictures of the new design were allowed or available during this trip.

The BSC-III cabinets were designed to place a gas-tight, leak-free physical barrier between the hazardous material and the laboratory workers, according to the BMBL. The cabinet line is inspected on a routine basis, and it meets the current CDC regulatory and BMBL guidelines. Cabinet modules were made of 11-gauge, type 304 stainless steel polished to nonglare satin finish in a unibody style with continuous welds that were ground smooth. This design eliminates all welding cracks, seams, ledges, and crevices that might harbor microorganisms. In addition, cabinets were fabricated with rounded interior corners (1/2-inch nominal radius) to permit easy and effective cleaning. Windows in the cabinet are made of 3/8-inch mirror-quality safety glass. Gloves are one-piece neoprene and can be replaced without loss of containment.

Class III cabinet performance is measured in terms of maintenance of adequate negative pressure balance, leak integrity, and filter integrity. The Class III cabinet line is maintained at a pressure differential of minus 0.5–0.8 inch water column (LSM, 1979) relative to the BSL-4 main lab area. This pressure differential is accomplished through the action of six independent cabinet exhaust fans connect by stainless steel ducts to the BSL-4 lab exhaust system, which is HEPA filtered before leaving the lab. The cabinet line is designed to provide an inward airflow of approximately

270 ft^3 per minute (cfm) in the event of a glove break in a cabinet module. Air moving through the cabinet modules pass through one HEPA filter before entering the cabinet and through dual-in-series HEPA filters before leaving the cabinet.

The original design of the cabinet line had eight individual modules (Figure 1.7-3). The BSC-III cabinet modules were arranged in order to facilitate the movement of materials safely in and out of the cabinet with minimal disturbance to work operations. This is consistent with the current design as well, although only the original 2 modules remain in the current configuration of the cabinet line. Cabinet modules can be isolated from the remainder of the cabinet line, without affecting the performance and containment of the other modules, by closing gas-tight gasket doors between modules. Cabinet leak integrity can be determined by mass spectrometry leak (MSL) testing to ensure the cabinet line has a gas-tight seal. Cabinets must not have a leak rate greater than $2x10^{-5}$ cc/sec of helium at positive 3 inches of water column pressure differential.

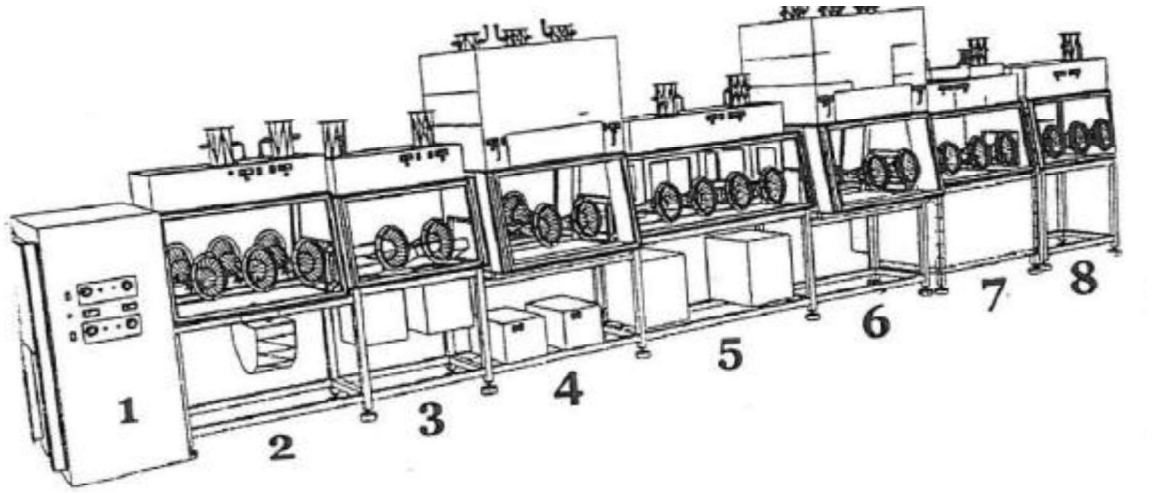

Figure 1.7-3. The original Class III cabinet line: (1) Autoclave; (2) working area with chemical dunk tank; (3) refrigerator and freezer; (4) to (6) mass airflow work stations for aseptic manipulations, where (5) has a compartment with an incubator; (7) inverted microscopy; and (8) small-animal housing.
[Source: Henkel, R.D, et.al.]

The cabinet line contains two types of modules based on airflow characteristics. Work areas in the cabinet line are designed as mass airflow modules, whereas the remaining cabinet units are turbulent airflow modules. The mass airflow modules are equipped with a ceiling-mounted HEPA filter above a stainless steel perforated diffuser. Return air slots are located in these modules at the work surface near the view screen. This design provides a top-to-bottom unidirectional airflow pattern of sterile air at a rate of 95 cfm. Since these work areas are used to manipulate cell cultures and sterile reagents, the ability to provide a directional flow of sterile air is an important design feature that reduces airborne contamination problems in the work area modules.

Cleaning and Sterilization Techniques

The facility has redundant inline HEPA air filters for air handling. The cabinet line has an autoclave module equipped with a Getinge sterilizer, which replaced the Steris Eagle 3023S sterilizer. Waste materials are heated at 132°C for 55 minutes before opening the outer door. A shorter autoclave cycle (132°C for 3 minutes) is completed when no waste materials are removed from the inner modules to decontaminate the empty chamber before the outer door is opened.

The BSC-III cabinet line and BSL-4 suite are decontaminated and recertified on an annual basis using VHP. All materials removed from the cabinet must be autoclaved, chemically inactivated, or sealed in double-walled airtight containers for transfer outside of the cabinet line and submerged in a glutaraldehyde dunk tank to chemically disinfect the exterior surfaces of the container for storage or transfer to another process.

All lab effluent waste is chemically and heat treated before leaving the facility. The waste is stored in concentrated bleach fiberglass tanks then loaded into a steam injection boiler at 110°C for 2 hours.

Instrumentation/Robotics/Unique Features

The original and current cabinet lines do not use robotics. There are various instruments and equipment associated with the cabinet line that must be manually accessed through various levers and gas tight doors. These include autoclaves, a refrigerator and freezer, mini tabletop centrifuges, water baths, incubators for cell culture, and an inverted microscope with a charge-coupled device (CCD) camera. The microscope, video cables, and power supply wiring are connected through hermetically sealed connection ports.

These unique features of the cabinet line demonstrate the full ability for all the work to be completed at BSL-4 level without ever breaking containment.

Lessons Learned

GSU's cabinet line is a state-of-the art unit that is effective at doing high-containment work. Working with BSC-III cabinet designers early is critical to developing a successful workflow. It is also important to understand instrument interfaces as early as possible as they effect workflow. The GSU cabinet line is static and cannot be moved without disconnecting HEPA filters and major construction. An alternative, more mobile-friendly cabinet design may be possible with early interaction from manufacturers.

GSU is moving into the next phase of high-containment lab work by building a BSL-4 suit lab. Due to the desire to expand the capacity to work with multiple pathogens at once and attract more scientists with specialized research projects, the university decided to move to a suit-lab direction. One major disadvantage of the cabinet line is that only one pathogen can be worked

on at a time. This inherently limits the ability of the lab to process multiple samples for fear of cross contamination.

Cost, Schedule, and Lifespan

Estimated costs for the original line was $3M with some modification needed for the existing infrastructure. The current cabinet line with custom equipment is approximately $1M, with operating costs of $500–700K per year. The new BSL-4 suit lab is estimated at $81M. The average lifespan of a BSL-4 containment building is about 20 years, although the cabinet line is surpassing that with regular updates to instruments and equipment.

To date, there have been no accidental breaches resulting in loss of containment or potential exposure to pathogens since these were built in 1998.

Summary

Overall, GSU's HCC is a unique world-renowned facility with expertise and perhaps infrastructure that could be leveraged in building and operating the SRF. The novel implementation of a BSL-4 cabinet line with instrument integration is a very attractive option for the SRF, considering the need for double-walled isolators with BSL-4 containment. More work and discussions are needed to understand future needs and requirements for proper implementation. Additionally, because of plans to build a new BSL-4 suit lab facility, there could potentially be areas where an MSR SRF could collaborate in the near and distant future.

Resources

Henkel, R.D., Sandberg, R.L., Hilliard, J.K. (2002). A Class III Cabinet BSL-4 Laboratory. In J.Y. Richmond (Ed.) *Anthology of Biosafety: V. BSL-4 Laboratories.* (pp. 237-252). Mundelein, Illinois: American Biological Safety Association

Operating a BSL-4 Laboratory in a University Setting: Georgia State University Lab Studies Deadly Alpha Herpes Virus; https://journals.sagepub.com/doi/pdf/10.1177/153567600501000408

1.8 Porton Down Public Health England (PHE): Salisbury, UK

Reason and Justification for Visit

Porton Down PHE is the UK's leading public health agency supporting all health emergencies and outbreaks. PHE has been instrumental in researching Ebola outbreaks and providing epidemiological services and screening. Research is primarily focused on the development of diagnostics and uses a single cabinet line laboratory (for BSL-4 pathogens) with some capability for performing small-animal studies. In an effort to investigate all technical trades for implementing a high-containment facility for the SRF, understanding the PHE glovebox cabinet line as a potential solution for dealing with Martian samples in high containment is critical.

Facility Description

The Porton Down site (Figure 1.8-1) was originally under the single ownership of the UK military. In 1979, the site was split, with part of it transferring into the health sphere as the Centre for Applied Microbiology & Research (CAMR) and operated as part of the Public Health Laboratory Service. Ownership of CAMR was transferred to the Microbiological Research Authority, a Special Health Authority, in 1994 where it operated until 2003, when it became part of the Health Protection Agency (HPA).

Figure 1.8-1. Exterior of Porton Down PHE in Salisbury, UK. *[Source:* www.dailymail.co.uk*]*

In 2013, the HPA was dissolved at Porton, and its functions transferred to PHE, an executive agency of the UK Department of Health. Today Porton PHE continues to research high-containment pathogens, respond to the UK's public health emergencies, and provide epidemiological services.

Containment Methods

The UK has both BSL-3 and BSL-4 laboratories. In the UK, these are referred to as Containment Level 3 and 4 (CL3 and CL4, respectively). Most of the work with dangerous pathogens is carried out in government and research council laboratories.

- CL3 labs
- CL4 *in vitro* cabinet line
- CL4 *in vivo* half-suit lab

Porton Down PHE has two types of CL4 containment laboratories: 1) an *in vitro* laboratory consisting of a cabinet line and 2) an *in vivo* laboratory where the primary containment is flexible half-suit isolators.

The *in vitro* laboratory is used for growth and enumeration of viruses and is where assays are performed. The *in vivo* / aerobiology laboratories are for animal infections and/or aerosol studies. Each laboratory has its own autoclave for sterilization. All laboratories run at negative pressure (>100 Pa) to the outside corridors and can be sealed for fumigation. The rooms undergo approximately 25 air changes an hour. Both inlet and exhaust air are double HEPA-filtered.

Alongside the CL4 laboratories, there are a series of airlock doors to maintain the negative pressure to the laboratory, as well as other rooms for changing and showering (separate showers for male and female per laboratory). The laboratories also contain an airlock for moving larger pieces of equipment in and out of the laboratory. Beyond the laboratories and associated rooms, there are two floors of air handling and engineering controls above the laboratory that supply and exhaust air to the rooms and cabinets and isolators. The floors above also allow some maintenance, such as changing lightbulbs, and access to electrical sockets, without entering the laboratories. There is a basement floor below the laboratories, which contains the effluent treatment facility that collects and treats all liquid waste coming from the laboratories and showers. The liquid waste is heat and pressure treated before being released.

In Vitro Cabinet Line

The single *in vitro* CL4 laboratory at Porton Down PHE is an airtight suite that contains a cabinet line made up of eight Class III microbiological safety cabinets connected to a single L-shaped spine (Figure 1.8-2). All virus manipulation is performed within the individual microbiological safety cabinets through gauntlets attached to glove ports. All cabinets and the spine run at negative pressure to the room (200–250 Pa) and have an air change rate of ~180 air changes an hour. The spine is more negative than the cabinets connected to it, thus reducing the risk of cross contamination between individual cabinets and allowing simultaneous work with multiple pathogens. Access to the cabinet line is via a disinfectant-filled dunk tank or a pass box that can

be independently fumigated/disinfected with formaldehyde vapor. The end of the cabinet line goes straight into a double-ended autoclave; access to the autoclave is on the clean side.

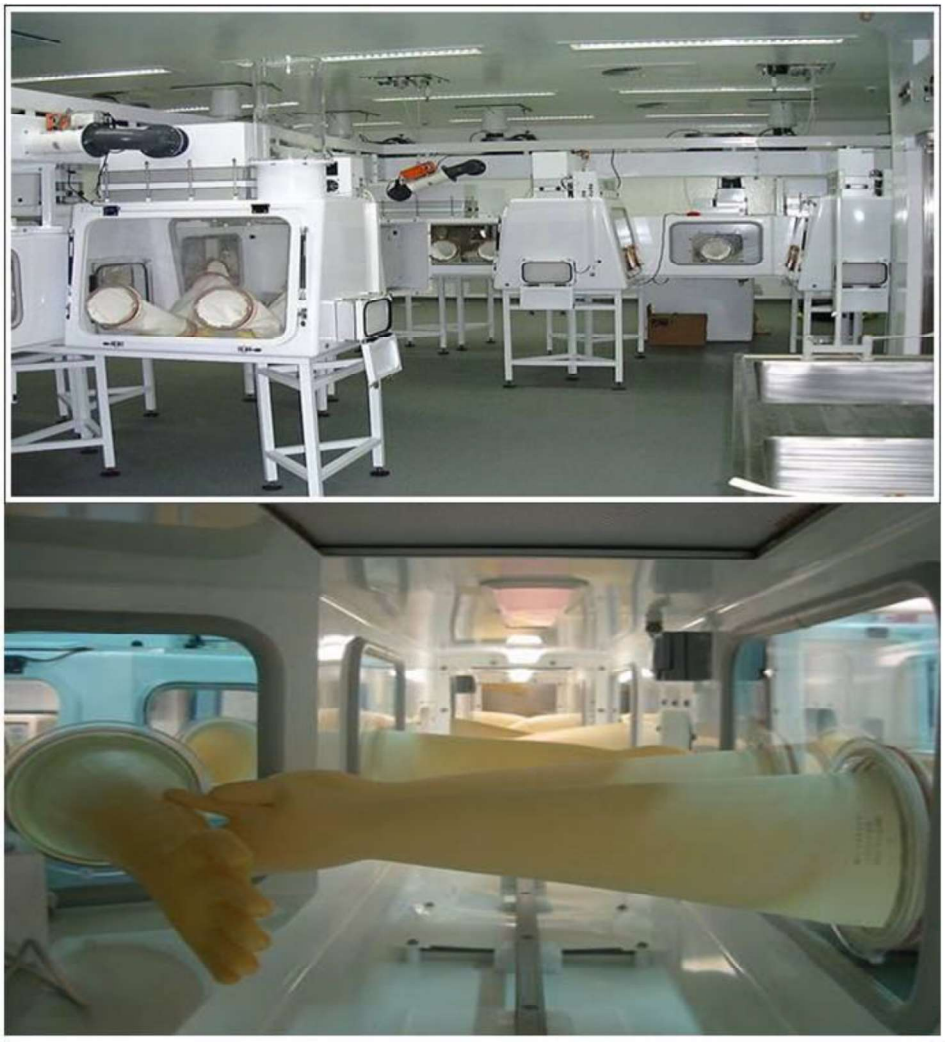

Figure 1.8-2. Porton Down PHE in vitro cabinet line CL4 laboratory with individual cabinets and attached with glove ports. (Continued on next page.)

Figure 1.8-2, Continued. Porton Down PHE *in vitro* cabinet line CL4 laboratory with individual cabinets and attached with glove ports. *[Source:https://www.healtheuropa.eu/phes-commerical-opportunities/96371/]*

Within the spine of the cabinet line, there are CO_2 incubators for growing viruses in tissue culture. Some of the individual microbiological safety cabinets are bespoke designs to house specialist equipment. There is a cabinet that contains an ultracentrifuge and another that contains several microscopes with the eyepieces on the outside of the cabinet. Also, within the individual cabinets are other pieces of equipment that may be needed such as benchtop or microcentrifuges, a real-time polymerase chain reaction (PCR) machine, and an ELISA plate reader. Equipment can be connected to an external computer via USB ports built into the cabinet walls. A trolley runs on a track up and down the spine to enable ease of movement between cabinets and incubators. The set up and validation of the cabinet line laboratory has been published.

In Vivo Half-Suit Lab

The purpose of this isolator line (Figure 1.8-3) is to allow complex animal or aerosol studies to go ahead while at all times maintaining an engineered form of primary containment between the pathogen and the workers. Animals are housed within the primary containment but can still be safely manipulated; all husbandry, exposures and infections, monitoring, and post-mortem analysis can be performed within the isolators. The isolators are maintained at negative pressure (c. 120–150 Pa) to the airtight room and undergo approximately 30 air changes an hour. This rate of 30 air changes an hour is considerably less than the 200+ in a microbiological safety cabinet, but this is for the benefit of the animals being held inside. With 30 air changes an hour, 5 minutes of ventilation will efficiently remove 90% of the circulating air, and 14 minutes is enough to remove 99.9%.

Figure 1.8-3. Porton Down PHE isolator *in vivo* half-suit CL4 laboratory.
[Source image from video: https://www.bbc.com/news/uk-48540653]

Similar isolator half-suits are being used in many laboratories for sterility assurance, encompassing a leak-tight enclosure equipped with means of transfer and manipulation in an enclosed environment. This mobile infrastructure allows cross protection of the operator/samples against microbiological and chemical contamination without compromising the environment. Getinge is a leading manufacturer of soft-wall half-suit isolators (Figure 1.8-4). Another example of a half-suit isolator (from Wickham Labs) illustrating suit connection and entry are shown in Figure 1.8-5.

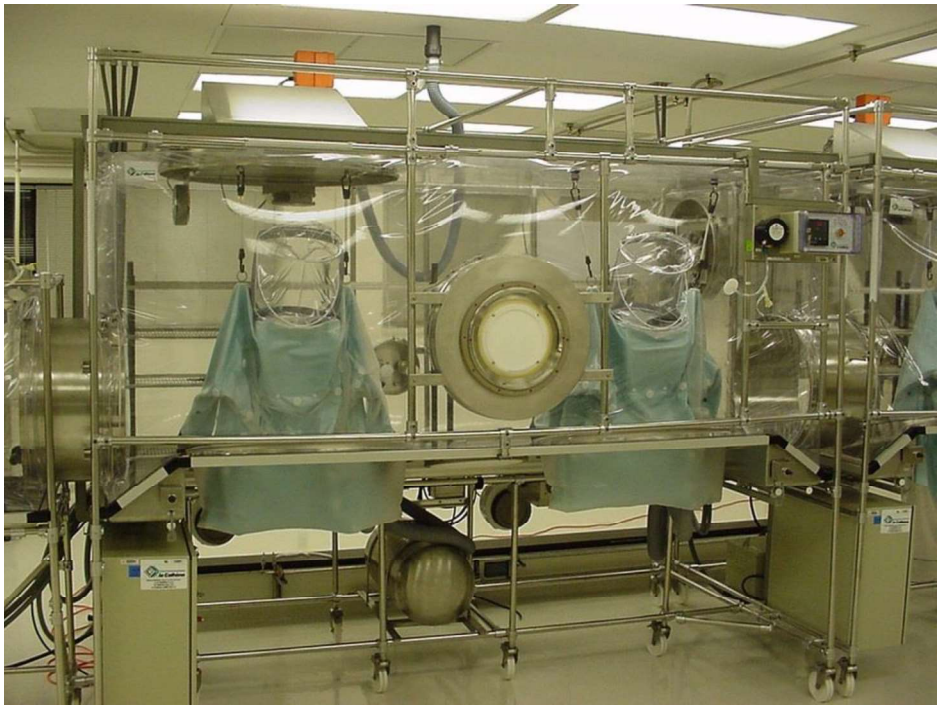

Figure 1.8-4. Getinge half-suit isolator, similar to those used in Porton Down PHE CL4 laboratory.
[Source: https://ardienconsulting.com*]*

Figure 1.8-5. Half-suit isolator examples showing suit connection and entry (from Wickham Labs). *[Source: Wickhamlabs.co.uk]*

Cleaning and Sterilization Techniques

The Porton Down PHE laboratories have redundant inline HEPA air filters for air handling. Critical facility systems have 100% backup and redundancy. The *in vitro* cabinet line uses vaporized formaldehyde, which is applied via a system of heaters that can be place throughout the cabinet line.

The *in vivo* half-suit lab has access to VHP or chlorine dioxide for decontamination and fumigation of working areas. Each laboratory has access to an autoclave for steam sterilization to inactivate some laboratory samples before exiting the lab.

Instrumentation/Robotics/Unique Features

Porton Down PHE is not currently using robotics except for high-throughput robotics for sample processing in some labs. The cabinet line has number of microscopes with the eyepieces on the outside of the cabinet while some cabinets have microcentrifuges, a real-time PCR machine, or an ELISA plate reader.

Lessons Learned

International regulations on BSL-4 differ from that in the United States. While most labs will follow guidelines in the BMBL for setting up high-containment laboratories, the regulations and standards for operation are different. There are no universal/international criteria used to select the placement of high-containment facilities. The location of BSL-3 and BSL-4 laboratories in the United States is part of an overall NEPA risk assessment that would consider other factors, including the availability of scientific and maintenance staff and proximity to emergency services. In the UK, they similarly concluded that after the correct risk assessment is undertaken and risk is managed appropriately, such recommendations would be treated on an individual basis. The

Health and Safety Executive (HSE) is the main government authority that regulates standards and compliance relating to general health, safety, and the environment, including most matters relating to biological agents, biosafety, and genetic modification. HSE fulfils advisory, regulatory, and enforcement roles.

The Advisory Committee on Dangerous Pathogens (ACDP) is the expert committee in the UK that works across various organizations, including HSE, PHE, and the Department for Environment, Food and Rural Affairs. The Control of Substances Hazardous to Health (COSHH) Regulations 2002 implements, for the UK, the European Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work.

In its current form, MSR is envisioned as an international campaign with the ESA, with the UK playing a major role. If it is envisioned that unsterilized MSR samples could be stored in a redundant European MSR facility, the SRF advanced planning should seek to harmonize requirements and regulations as best as possible to avoid potential delays or issues with sample transfer between facilities. Each regulation for containment and logistical operations may be different between Europe and the United States, which could impact the containment or cleanliness of the returned samples, so effective communication on requirements needs to be undertaken to mitigate the potential for this occurrence.

Cost, Schedule, and Lifespan

The cost of the *in vitro* cabinet line is unknown at this time as it was implemented in the 1970s. No breaches of containment have been reported. With routine maintenance of air filters and replacement of gasket seals and gloves, the lifespan of the cabinet line is expected to last for years, possibly decades.

Summary

The Porton Down PHE is the UK's leading public health agency supporting all health emergencies and outbreaks. The *in vitro* cabinet line and *in vivo* half-suit laboratories offer a unique perspective on implementing biological containment. While the lab is not primarily focused on sample cleanliness, half-suit isolator technology has been routinely used to maintain aseptic techniques and could offer a novel solution for MSR handling.

Resources

Lever, M.S.; Howells, J.L.; Bennett, A.M.; Parks, S.; Broster, M.G. The microbiological validation of a new containment level 4 cabinet line. J. Appl. Biosaf. 2008, 13, 98–105; https://www.researchgate.net/publication/266273022

Smither, S.J. and Lever, M.S. A Review of Filovirus Work and Facilities at The Defence Science and Technology Laboratory Porton Down. Viruses. 2012, 4, 1305-1317; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3446764/

National Academy of Sciences and National Research Council. Biosecurity Challenges of the Global Expansion of High-Containment Biological Laboratories: Summary of a Workshop. Washington, DC: The National Academies Press. 2012, E8, 175-204. https://www.nap.edu/catalog/13315/

Porton Down Programme for NASA Visit 7th Feb 2020

1.9 Germfree Laboratories Inc. (Modular Manufacturer): Ormond Beach, FL

Reason and Justification for Visit

Germfree is a premier manufacturer of mobile and modular biocontainment and aseptic facilities, serving clients globally. Germfree also manufactures custom containment equipment, including BSC-III cabinets (gloveboxes) that are used in more than half of all BSL-3/4 facilities across the globe. In an effort to explore different types of construction methods for NASA's MSR receiving and curation facilities, our team chose to visit Germfree to better understand the state of technology for constructing mobile and modular BSL-4 facilities. In addition, Germfree has extensive experience with designing and fabricating custom BSC-III cabinets that potentially could be leveraged for developing primary containment for MSR.

Facility Description

Germfree was founded in 1962 by Dr. Jerome Landy, a prominent Chicago and Miami surgeon who invented some of the first isolators and contamination control devices for hospitals in the 1950s and 1960s. In 1967, Germfree was contracted by NASA to provide the Apollo program with biosafety isolators/gloveboxes used in Lunar Receiving Lab JSC Building 37 for conducting biohazard assessment of lunar material. In the 1970s, Germfree received patents on their Class II and III biosafety cabinet designs and continued to innovate into the pharmaceutical processing lines in the 1980s. In 1999, the first mobile biological and pharmaceutical labs were introduced into the market, and this was fed forward into the full production of modular facilities in 2007. As of 2016, Germfree is located in a new manufacturing facility with 173,000 ft^2 of manufacturing space with approximately 200 employees in Ormond Beach, Florida (60 miles north of Kennedy Space Center). The company provides the following products and services by application:

- Hospital pharmacy
  - Stainless steel compounding aseptic isolators
  - Stainless steel radiopharmacy equipment
  - Stainless steel laminar flow hoods
  - Stainless steel Class II biological safety cabinets
  - Cleanroom pass-through boxes
  - Turnkey modular compounding pharmacies
  - Rental compounding trailers
- Analytical laboratory
  - BSC-III cabinets (total system integration, The SEA-III, aerobiology, and all hazard receipt)

  - BSC-II cabinets (Class II Type A biosafety cabinets, Class II Type B biosafety cabinets, custom portable and transportable Class II biosafety cabinets, and robotic safety enclosures)
  - Fume hoods
  - Class I BSC / lab enclosures
  - Laminar flow & PCR
- Mobile laboratory facilities
  - bioGO BSL-3 mobile biocontainment laboratory
  - bioGO 24’ BSL-2 mobile biocontainment laboratory
  - bioGO 53’ BSL-2+ mobile biocontainment laboratory
  - Rental cleanrooms & cGMP trailers
  - Trailer laboratories
  - Truck laboratories
  - Van laboratories
  - Mobile container labs
  - Air/C-130 transportable
- Modular laboratory facilities
  - BSL-3 laboratories (integrated modular BSL-3 buildings, international containerized BSL-3, and BSL-3 heating, ventilation, and air conditioning [HVAC] mechanical suite)
  - BSL-2 and BSL-2+ labs
  - bioGO 40’ ISO container BSL-3 laboratory building
  - TB laboratories
  - BSL-3Ag & BSL-4 capabilities
  - ABSL-3 laboratories
  - Rental/immediate response
- BioPharma production facilities
  - bioGO mobile cleanrooms and cGMP production
  - bioGO modular pharmaceutical facilities
  - Pharmaceutical isolators & RABS
  - Pharmaceutical laminar flow equipment

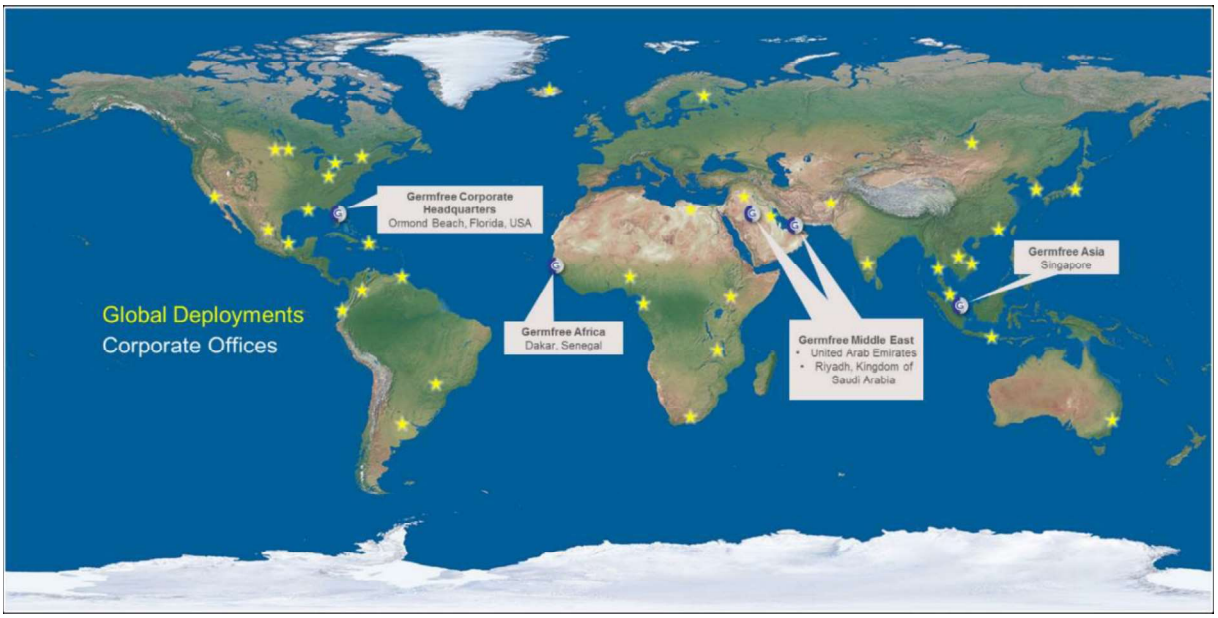

Figure 1.9-1. Germfree's mobile and modular facility deployment and offices. *[Source: Germfree]*

All Germfree facilities (Figure 1.9-1) and equipment are designed and manufactured at their facility in Florida. The company has several field offices around the world as well as significant experience with global deployment.

Containment Methods

Germfree specializes in three containment product lines that could be useful for a future MSR receiving and curation facility: 1) Class III biosafety isolators/gloveboxes, 2) mobile biocontainment laboratories, and 3) modular biocontainment facilities.

Figure 1.9-2. Integrated Class II BSC, Class III BSC/glovebox, and Class I fume hood. *[Source: Germfree]*

BSC-III Isolators/Gloveboxes

Germfree has extensive experience building biosafety cabinets (Figure 1.9-2) for over 50 years and were the company of choice for the Apollo program biohazard testing of moon rocks. Our team also saw their BSC-III gloveboxes installed at USAMRIID and Galveston National Lab. In addition, they have experience building complex containment lines for pharmaceutical manufacturing, including bio-decontamination capabilities. While Germfree has experience constructing gloveboxes for clients that would integrate robotics into isolators, Germfree does not currently have experience in the actual integration of robotics into their isolators/gloveboxes. In addition, while they have built isolators for radiopharma, they have not built any gloveboxes or isolators for the nuclear industry.

Mobile Biocontainment Laboratories

Figure 1.9-3. Germfree BSL-3 trailer laboratory (disease surveillance and identification laboratory for King Abdulaziz University Hospital, Saudi Arabia). *[Source: Germfree]*

Germfree provides their clients with a turnkey product for mobile laboratories from design/space planning to engineering and manufacturing. They also provide full testing, transportation, installation, commissioning, and certification of all of their mobile labs (Figures 1.9-3, 1.9-4, and 1.9-5). In addition, the company offers initial training, continuing training, and ongoing maintenance plans.

Figure 1.9-4. Defense Research and Development Canada (DRDC) deployed a Germfree 42-ft trailer for a chemical analysis laboratory equipped with shock-mounted GC/MSs for chemical sample analysis and high-containment sample receipt laboratory. *[Source: Germfree]*

Figure 1.9-5. 24-ft CL3 (BSL-3) hybrid container/trailer laboratory designed for C-130 air-transport used by Public Health Agency of Canada (PHAC). *[Source: Germfree]*

Modular Biocontainment Laboratories

Germfree has recently started marketing a modular biocontainment lab platform called: bioGO that is "offsite built and containment ready" (Figure 1.9-6). These modular facilities can be built and made operational faster than any facility built using traditional brick-and-mortar construction methods. Each module is built inside a factory with installation of floor, wall, ceiling, and door systems. The space is then fitted for turnkey technical equipment per application, bio-decontamination systems, access controls and monitoring, and building automation systems. The modules are then fitted together and fully tested and commissioned before being shipped for installation in the field. Germfree uses their proprietary technology for bio-sealing between modules to allow for fully sealed facilities of any size by connecting multiple modules together. This construction method mitigates project risk by allowing for complete factory quality control and testing of HVAC and pressurization control. The bioGO platform is intended to be a durable and permanent construction with standard and highly customized configurations. Germfree also provides all design, engineering, construction, and in-field full service support.

Figure 1.9-6. Germfree's bioGO construction schedule comparison between modular vs. brick-and-mortar construction. *[Source: Germfree]*

- Bio-containment laboratories
  - BSL-2, -3, -3AG, -4
  - Negative pressure
  - BSCs and other equipment
- cGMP cleanrooms
  - BioPharma applications
  - ISO 8, 7, and 5 classifications
  - Positive- and negative-pressure modes
  - Isolator, RABS, laminar flow equipment

- Rx compounding cleanrooms
  - 503B and compounding pharmacy
  - ISO 8 and 7 classifications
  - Positive- and negative-pressure modes
  - Primary engineering controls included
- Facility platform configurations
  - Single or multi-module “box in a box” with sizes up to 14’W x 60’L: Placed into a shell building, and modules size based on requirements
  - Single or multi-module free standing with sizes up to 14’W x 60’L: Placed outdoors, and modules size based on requirements
  - Trailer-based cleanroom with sizes up to 53’: Fully mobile and rental fleet available

Figure 1.9-7 shows Germfree manufacturing mobile laboratories. Figures 1.9-8 and 1.9-9 show Germfree manufacturing modular bioGO laboratories.

Figure 1.9-7. Germfree manufacturing mobile laboratories. *[Source: Germfree]*

Figure 1.9-8. Germfree manufacturing modular bioGO laboratories. *[Source: Germfree]*

Figure 1.9-9. Germfree manufacturing modular bioGO laboratories. *[Source: Germfree]*

Germfree built an ABSL-3 facility for Duke University and the National University of Singapore (Duke-NUS) Medical School in Singapore, which is described in the next section. Several modular containers were constructed, assembled, and tested by Germfree in Florida. After final pressure testing, the modular facility was disassembled into individual pieces and shipped to Singapore to be reassembled and installed into a shell building. The building was again pressure tested, commissioned, and granted operational status within one month. Figure 1.9-10 shows one of the modules being lowered into place and the shell building that was built around it. This modular facility is scheduled to be moved again to the roof-top of an existing building in 2021. Germfree suggests that with the addition of a high-temperature effluent decontamination system (EDS), breathing air for BSL-4 suits, and chemical showers for BSL-4 suit decontamination, they could make a facility that would meet BSL-4 requirements based on this platform technology.

Figure 1.9-10. Duke-NUS facility in Singapore.
Module being lowered into place (left). Shell building built around the modules (right). [*Source: Germfree]*

Cleaning and Sterilization Techniques

N/A

Instrumentation/Robotics/Unique Features

N/A

Lessons Learned

N/A

Cost, Schedule, and Lifespan

N/A

Summary

Germfree offers an impressive line of mobile and modular containment facilities. While they have never designed a BSL-4 mobile or modular lab, they have indicated that they are ready for the challenge and the technology exists to quickly manufacturer and commission such a facility faster than one using traditional brick-and-mortar construction. Technology is shared between the modular construction methods and mobile within their manufacturing process, therefore this is not a large step. Germfree gloveboxes for biocontainment have been used for the past 50 years, and we saw them in operation at many BSL-4 labs. However, Germfree may lack experience in robotic and automation integration into gloveboxes when compared with companies such as Comecer. However, Germfree is interested in developing this robotic technology and would invest in the necessary expertise to make this successful.

Resources

Germfree presentation “BSL-4 Modular”
Germfree presentation “NASA – Germfree Mobile Laboratories”

1.10 Duke University and the National University of Singapore (Duke-NUS) ABSL-3+ Modular Facility: Singapore, Singapore

Reason and Justification for Visit

The ABSL-3 modular facility located in Singapore is an advanced permanently deployed modular biocontainment facility. In an effort to explore different types of construction methods for MSR receiving and curation facilities, we selected to evaluate new types of modular BSL-4 facility designs over traditional brick-and-mortar containment construction. Currently, there are no BSL-4 modular facilities constructed in the world; however, this modular facility in Singapore manufactured by Germfree is the closest match to BSL-4 design requirements.

Facility Description

Duke-NUS Medical School in association with the Singapore government developed the first ABSL-3 facility in Singapore (Figure 1.10-1). Since 2014, this Duke-NUS ABSL-3 facility has provided Singapore with research capabilities in emerging diseases for outbreak preparedness and a center for international research collaboration in Southeast Asia. The facility is designed to conduct biological and infectious disease studies with mainly rodents and nonhuman primates. Germfree was contracted by NUS to design a cost-effective BSL-3 modular facility. Several modular buildings were constructed, assembled, and tested by Germfree between 2013 and 2014 in Florida. After final pressure testing, the modular facility was disassembled into individual pieces and shipped to Singapore. After the modular lab components and other ancillary equipment arrived in Singapore, the facility was reassembled and installed into a shell building. After installation, the building was again pressure tested, commissioned, and granted operational status within one month. This current facility is now scheduled to be relocated to another part of the city closer to the medical school. The modular facility will be disassembled and reassembled in a shell building located on a roof of an existing NUS building. The modular flexibility and quick commissioning result in a much faster schedule than traditional brick-and-mortar construction.

Figure 1.10-1. ABSL-3 modular facility in shell building in Singapore (left). Modular facility constructed and tested in Florida (right). *[Source: Germfree]*

Containment Methods

The interior of the modular ABSL-3+ facility (Figure 1.10-2) is constructed with four modules (48 ft long by 14 ft wide by 12 ft high) and one 40 ft ISO shipping container that houses the HVAC, electrical, and other facility systems. The modules are bolted together and sealed with large gaskets to create a hermetic seal inside a shell building constructed out of steel I-beams and insulated corrugated metal (non-conditioned space). After modular containers are in-place, the complex HVAC ducting is fitted together on top of the containers and the electrical, plumbing, and facility controls are attached. The four-container facility is divided into three main labs:

- Lab 1: BSL-2 molecular lab space
- Lab 2: BSL-3 lab space includes necropsy work area, autoclaves, tissue digester, and separated nonhuman primates housed in open cages (max. six)
- Lab 3: BSL-3 lab space includes additional space and rodents housed in isolated cages

The layout (Figure 1.10-3) shows the first module as the main entrance, housing a small office/monitoring control room and bathroom. Adjacent to the main entrance, personnel enter an anteroom with separated lab entrance and exit doors. All doors in the facility are equipped with interlock air pressure doors with inflatable gaskets. These doors are similar to other BSL-4 lab interlock doors with inflatable silicone gaskets; however, the doors are about a quarter of the thickness and weight. The lab entrance goes to a change room / hallway where personnel can change into scrubs. After this area, the lab has two separate gowning rooms for donning PPE: one to enter a BSL-2 lab area and one to enter into the BSL-3 lab area, which requires more PPE. After the scrub change room / hallway, the lab entrance also allows access to a hallway that can access waste generated from the autoclaves and a back entrance. All sterilized waste is removed through the back-entrance door. Once in the BSL-2 or BSL-3 lab areas, personnel exit through a shared hallway on the opposite side of the facility to a gender-separated decontamination shower area and exit.

Figure 1.10-2. Facility interlocking door with inflatable gaskets and monitoring displays/alarms (left). BSL-3 lab area with autoclaves, tissue digester, and downdraft table (right). It also shows the mating seam between two modular containers. *[Source: Germfree*)

The PPE for BSL-2 is scrubs, lab coat/smock, lab shoe covers, gloves, and safety glasses. The PPE for BSL-3 lab areas is scrubs, full coverall suit, inner and outer boots, double gloves, and full-face shield/hood with PAPRs. The control room can continually monitor door interlock system, room-to-room differential pressure of the entire facility, intercom system, and video cameras located throughout the facility. In addition, all rooms have screens with these monitoring parameters as well as traditional safety alarms system notifications.

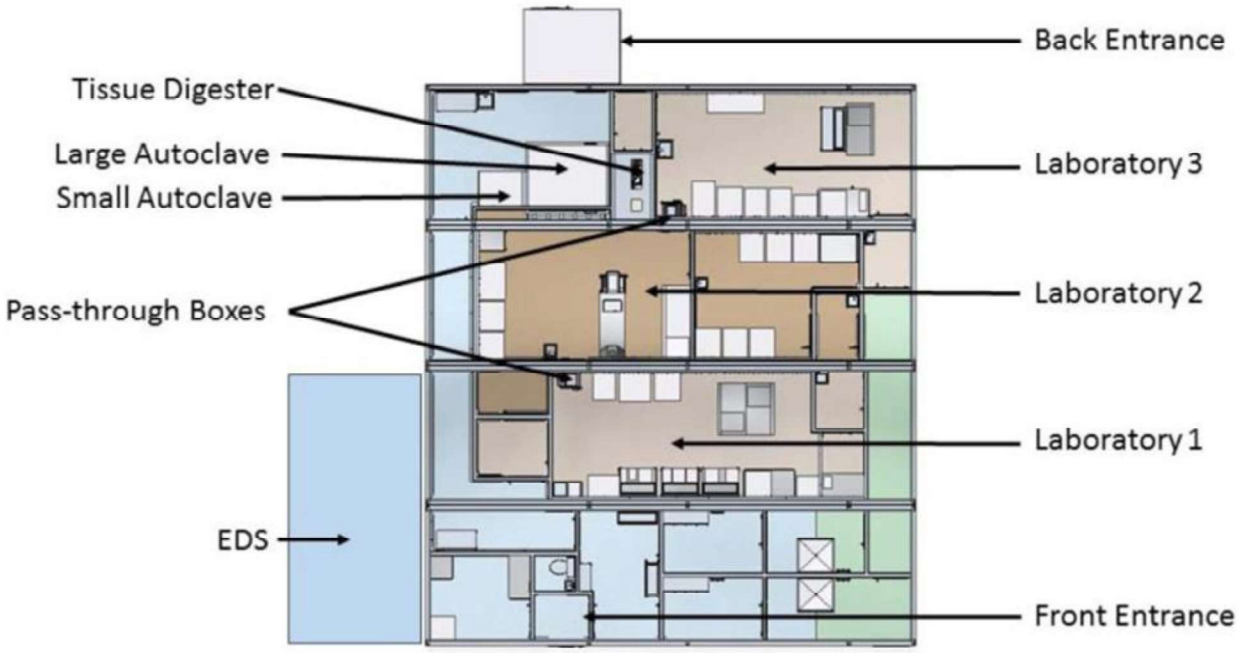

Figure 1.10-3. Singapore facility layout. *[Source: figure modified from Vijayan, V., & Ng, B. (2016). Validating waste management equipment in an animal biosafety level 3 facility. Applied Biosafety, 21(4), 185-192.]*

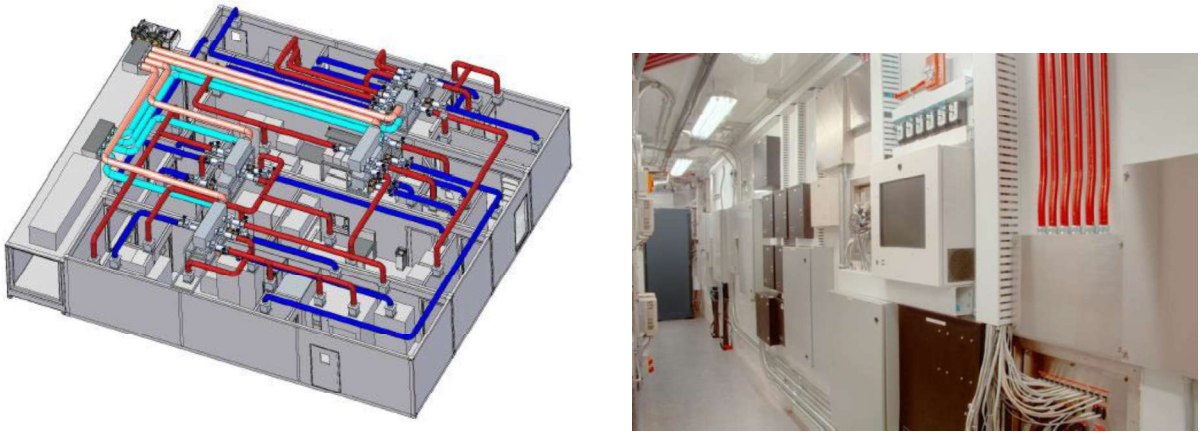

Figure 1.10-4. HVAC system CAD drawing (left). Mechanical room (right). *[Source: Germfree]*

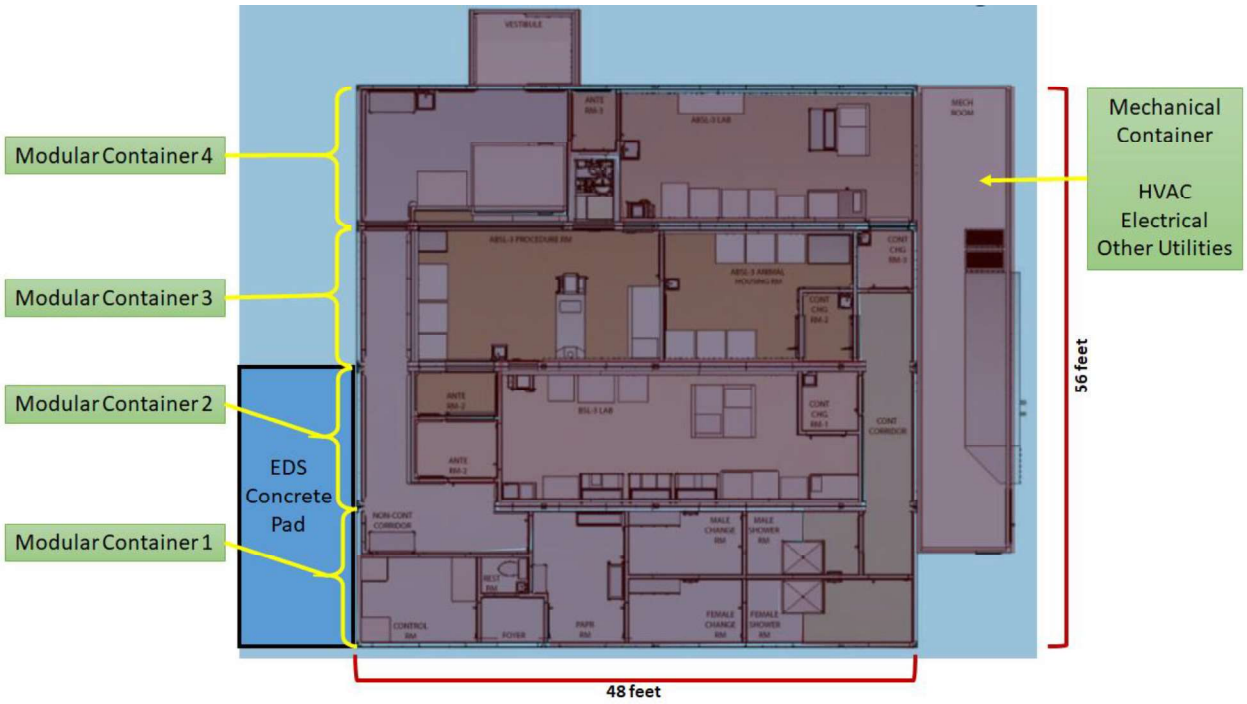

Figure 1.10-5. Modular containers 1–4 locations relative to the EDS and mechanical container.
[Source: Image modified from Germfree]

Cleaning and Sterilization Techniques

The laboratory is equipped with two autoclaves and one tissue digester. The large autoclave (MMM Vakulab PL Steam Sterilizer) is sized to decontaminate nonhuman primate cages when required. The small autoclave (MMM Sterivap HP IL Steam Sterilizer) is routinely used for solid waste, rodent cages, lab tools, and laundry. The facility was designed with two autoclaves to serve as redundant systems in case of failure. The tissue digester (Bio-Response Solutions TDPL) is used to decontaminate animal carcasses, parts, and other remains. The autoclaves and tissue digester can only be accessed from the main lab. Any waste generated from Lab 3 or Lab 1 is required to be sent through the wall pass-through system into Lab 2 to be decontaminated.

The EDS (Bio-Response Solutions EDS Chemical Batch Decon) is located outside of the main facility containment and constructed on a concrete foundation (no modular container was constructed). All wastewater from the showers, laboratory sinks, and downdraft table is transported under the facility containment containers to the EDS through double-walled pipes. These ABSL-3 waste management designs were formulated from the guidelines generated by the World Health Organization's laboratory biosafety manual requirements.

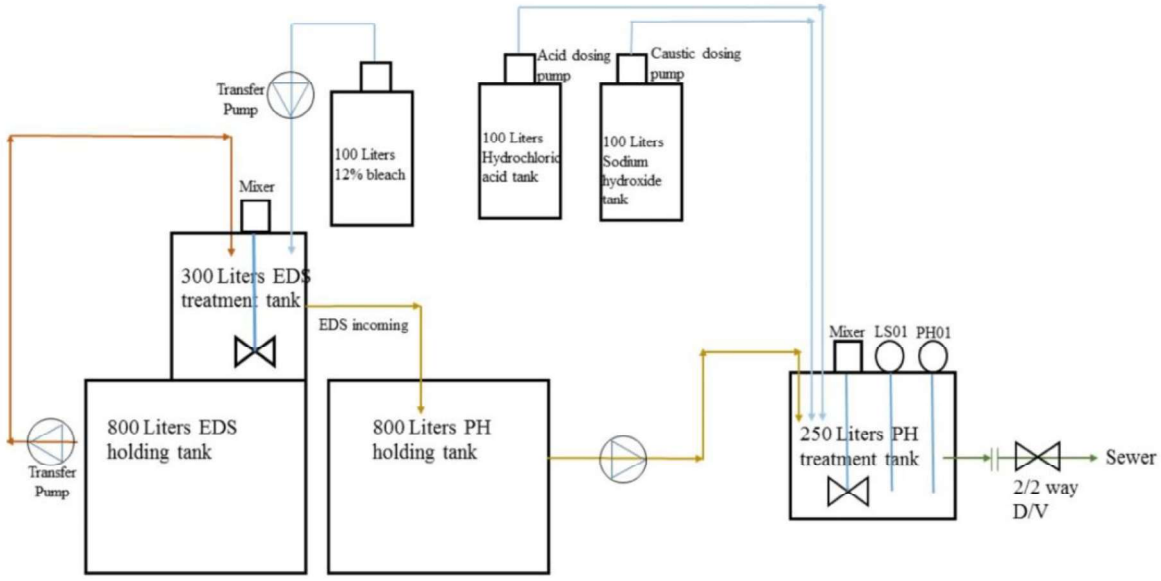

Figure 1.10-6. EDS system. *[Source: Vijayan, V., & Ng, B. (2016). Validating waste management equipment in an animal biosafety level 3 facility. Applied Biosafety, 21(4), 185-192.]*

The rooms are decontaminated with VHP with portable generators that are moved around the facility, plugging into ports in each room.

The need to do testing with biological indicators for all their sterilization and decontamination processes was emphasized.

Instrumentation/Robotics/Unique Features

N/A

Lessons Learned

The Singapore government requires that the facility be certified annually. This annual certification includes a required negative-pressure test, at -1000 Pa or ~10 times the normal operating negative pressure for the facility. All container mating joints, doors, and other facility connections are tested for leaks. This pressure test loads the structure annually and may reduce the lifespan of the gaskets and use of the facility when compared to facilities that only test once at facility commissioning. However, the facility continually passes leak testing, which is a positive indication of the long-term viability of this modular facility.

This modular facility will be moved in 2022 to a new location in Singapore on an existing building's roof (three stories high). This facility will have good lessons learned for relocating existing modular facilities. The plan is to currently crane each container to the roof and secure them together. Afterward, a shell building will be built around the facility to protect the HVAC ducting and other utility structures (Figure 1.10-7).

Figure 1.10-7. Germfree's architectural design for relocating the Duke-NUS ABSL-3 facility in Singapore to a new roof location (left before, right after). *[Source: Germfree]*

The only systems that are missing from the ABSL-3 lab in Singapore that would make this facility meet BSL-4 requirements are the following:

- High-temperature EDS
- Breathing air for BSL-4 suits
- Chemical showers for BSL-4 suit decontamination

Germfree noted that all of these systems are currently available as commercial off-the-shelf (COTS) and could be integrated into the Singapore ABSL-3+ lab design. In addition, Germfree has experience with each of these systems and has full confidence in their ability to integrate them into a modular BSL-4 laboratory.

Cost, Schedule, and Lifespan

The lifespan was planned to be 10 years, before refurbishment of the facility.

The construction schedule was a 6-month design, 12-month build, and 3-month installation and commissioning.

Summary

The Duke-NUS ABSL-3 facility demonstrates that modular construction is an option for designing a BSL-4 containment facility for MSR. There are many attractive aspects of such a modular facility in terms of lower costs and compressed schedule for building and commissioning. However, this facility still required a shell building to be constructed that was designed with a 30+ year lifespan before major maintenance activities. This type of modular containment design has not been widely chosen or used in the biocontainment community and may require additional designs and testing to prove equal to traditional brick-and-mortar biocontainment structures.

Resources

Duke-NUS_ABSL-3_Facility_Video. https://youtu.be/eC1dvAcefjQ

Validating Waste Management Equipment in an Animal Biosafety Level 3 Facility. https://journals.sagepub.com/doi/10.1177/1535676016666359

2 Pristine Facilities

2.1 Japan Aerospace Exploration Agency (JAXA) Hayabusa and Hayabusa2 Curation Cleanroom Laboratories: Sagamihara, Japan

Reason and Justification for Visit

JAXA's astromaterials curation laboratories are equipped with highly customized, state-of-the-art clean chambers for processing astromaterial samples from the Hayabusa and Hayabusa2 missions. Since the inception of the first Hayabusa mission, NASA has had an exceedingly successful and collaborative working relationship with JAXA. The visit was timed to allow access to the laboratory and scientist/technicians without causing undue burden given the ongoing processing of Hayabusa samples and active Hayabusa2 mission.

Facility Description

Formerly known as the Planetary Material Sample Curation Facility (PMSCF), the Extraterrestrial Sample Curation Center (ESCuC) in Sagamihara, Japan houses JAXA's astromaterials collections, present and future. The original facility was completed in 2008, with conceptual studies for the facility beginning in 2005 to prepare for the Hayabusa sample return mission. However, before Hayabusa even returned, plans for the next sample return mission (Hayabusa2) began. This new mission required the construction of its own cleanroom. Non-cleanroom space utilized for the Hayabusa mission was renovated to accommodate the new collection. Each collection will be stored and processed in their own isolating chambers/gloveboxes and cleanroom. However, due to personnel limitations, once Hayabusa2 samples return, the first Hayabusa mission's samples will not be processed or allocated during the preliminary examination phase of Hayabusa2.

The Sagamihara campus itself was open in 1989 as the main facility of the Institute of Space and Astronautical Science (ISAS). This research center provides graduate education programs for researchers and engineers. As an inter-university research institute, it is a hub for researchers from across Japan and the world to gather to perform a variety of research projects.

Figure 2.1-1. JAXA ISAS Sagamihara campus. ESCuC is located within the Research/Administration Building. *[Source: JAXA]*

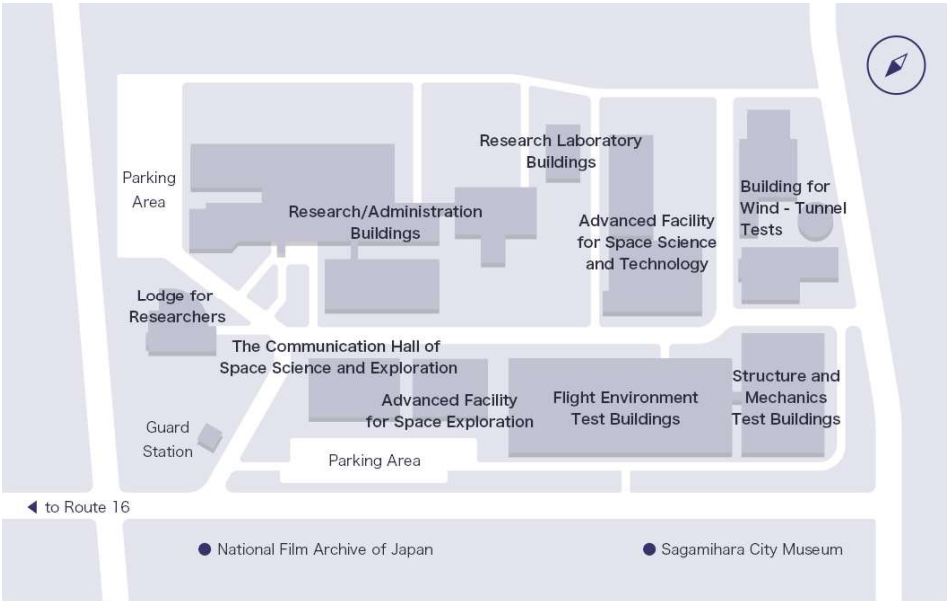

Figure 2.1-2. JAXA ISAS Sagamihara campus map. *[Source: JAXA]*

Containment Methods

JAXA's ESCuC laboratory suite utilizes positive-pressure cleanrooms, gloveboxes, and clean chambers to process and store the Agency's astromaterial collections, utilizing Hitachi technology throughout the project. Working inward, the laboratory consists of five different cleanrooms, ranging from ISO 5 (Class 100) to ISO 7 (Class 10,000): two planetary sample handling rooms (ISO 5–6), an electron microscope room (ISO 6), a sample preparation room (ISO 6), and a

manufacturing and cleaning room (ISO 7). The cleanroom suites utilize 90% returned filtered air with the layout of the laboratories, allowing for cascading pressures to help manage contamination. While all laboratories have vertical laminar flow, cleanrooms classified at ISO 5–6 have a raised flooring system and additional chemical filters above the HEPA banks to ensure mission contamination control requirements are satisfied. For more details about the cleanroom designs, please see Yada et al. 2014 and McCubbin et al. 2019.

JAXA worked with Hitachi Group and MIWA Manufacturing to design and construct the clean chambers (CCs) and tooling for both Hayabusa and Hayabusa2 missions. Hitachi focused on the vacuum isolator chambers, and MIWA focused on positive-pressure glovebox isolators. Due to the nature of the samples, the CCs are highly customized. To limit contamination, the construction materials were highly controlled. The bulk of the chambers are constructed of 304 and/or 316 stainless steel, but aluminum, A6061 aluminum alloy, quartz glass, PTFE, and Viton were also used. The inside walls are electropolished and then baked in vacuum to ≥120 °C before and after installation. The glove ports are equipped with Viton gloves. However, although state-of-the-art, efforts were made to not "over-engineer" the chambers. Consequently, where possible, the most streamlined option was chosen. The outcome of this design not only decreased regular maintenance and downtime from repairs, it also decreased the cost because manual controls are used instead of automation. Part of the custom design allowed for designated chambers to alternate between ultrahigh vacuum and positive-pressure pure dry nitrogen environments, while part of the chambers was also specifically designed to allow for the flight sample container to be fully integrated (Figures 2.1-3 and 2.1-4). This integration allowed the sample catcher/container to be opened within the highly controlled CC environment while not compromising the cleanliness within the chamber itself. Please see the list of links to Hitachi Brand Channel's description of the CCs and cleanroom technology within the Resources section.

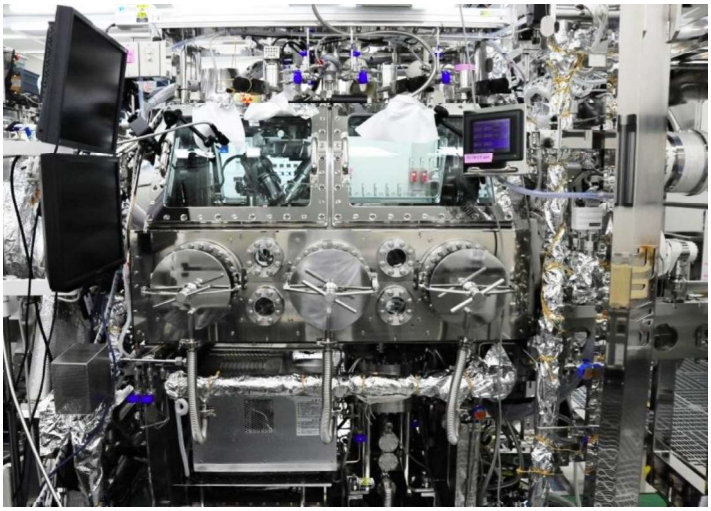

Figure 2.1-3. Cleanroom chambers utilized for Hayabusa. *[Source: JAXA]*

Learning from practical experiences gained while storing and processing Hayabusa samples, the CC developed for Hayabusa2 has increased its chambers from two to five. Most of the expansion was focused on capabilities in ultrahigh vacuum, although there is an additional processing chamber with an optical window on top of the chamber (CC4-2). The CC4-2 flat window can accommodate better viewing and sample handling, as well as a custom microscopy instrumentation. Keeping the microscopy system outside of the CC4-2 mitigates any material cross-contamination. As with the first chamber in the Hayabusa CC, CC3-1 is designed to directly connect with the flight sample container, allowing for the samples to be open in vacuum. Once opened, the samples are then transferred to CC3-2, which allows for samples to be handled under vacuum. When additional processing is necessary, the sample is then transferred to CC3-3, where the sample handling environment will change from vacuum to purified dry nitrogen.

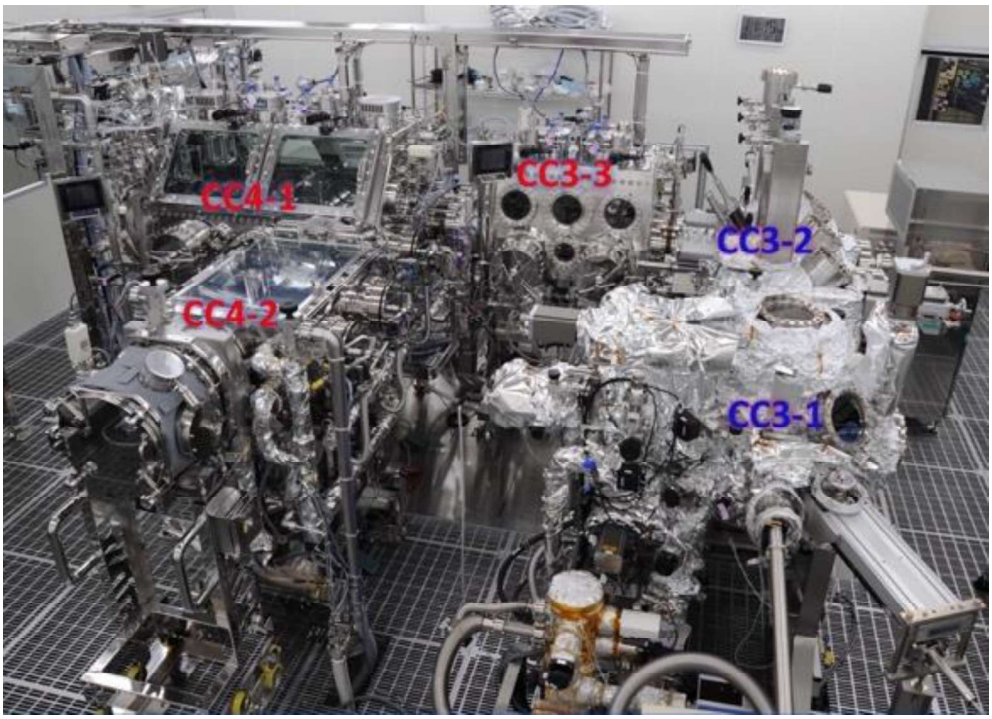

Figure 2.1-4. Hayabusa2 sample-handling system.
The system consists of five chambers: CC3-1, CC3-2, CC3-3, CC4-1, and CC4-2. Chambers labelled CC3 have high vacuum capability. Chambers labelled with red text have a dry, purified nitrogen environment. Chamber CC3-3 interchanges between a vacuum and purified nitrogen environment. *[Source: JAXA]*

Hayabusa extracts captured gas from their capsule soon after landing and sends it to multiple labs for analysis. This may be a good model for extracting the gas samples from MSR and should be explored further.

Cleaning and Sterilization Techniques

The high organic content of the samples from Hayabusa, Hayabusa2, and OSIRIS-REx require a high level of organic cleanliness and sterility. The CCs are designed to withstand two ≥120 °C bakeouts before samples are introduced. For equipment and tools required for sample processing, there is a multiple-stage cleaning process that gets more stringent depending on the material and if it is going to directly touch the samples.

Instrumentation/Robotics/Unique Features

The CCs are perhaps the most unique equipment within the ESCuC, with the CC for Hayabusa2 being an expanded version of the one constructed for Hayabusa. The integration of vacuum and pure nitrogen environments, use of three digital microscopes (two mounted within the cabinet and one mounted externally), and micromanipulator-assisted particle transfers enable the processing of individual particles that are highly susceptible to contamination and too small for traditional tweezers. The integrated mechanical manipulation system was manufactured by Hitachi and utilizes the electrostatic properties of the particles to their advantage (Yada et al. 2014).

The facility also features a wide variety of instrumentation, including X-ray computed tomography / X-ray diffraction (XCT/XRD), transmission electron microscope / scanning electron microscope (TEM/SEM), electron probe micro-analyzer (EPMA), secondary-ion mass spectrometry (SIMS), Fourier-transform infrared spectrometer (FTIR), Raman spectrometer, neutron activation analysis (NAA), noble gas mass spectrometer, and time-of-flight secondary-ion mass spectrometer (ToF-SIMS).

Lessons Learned

The Hayabusa2 isolating chambers are more complex. Please see previous sections for details.

For Hayabusa2, a vacuum environment is preferred for pristine primary containment, and a positive-pressure nitrogen environment is preferred for handling the actual asteroid samples. During the first Hayabusa mission, a lesson learned by JAXA was that handling samples in a vacuum became difficult and was troubled by mechanical problems. This experience was similar to the problems of the high-vacuum complex used by Apollo 11 and 12.

Cost, Schedule, and Lifespan

The planning and design phase of the original ESCuC facility began in 2005. Construction then began early in 2007 and was completed in 2008. After construction was complete, a year's worth of functional tests were followed by another year of rehearsals. The Hayabusa space capsule was recovered from the Australian outback on June 14, 2010. In 2015, plans began for the Hayabusa2 mission. Part of the facility was remodeled to accommodate the Hayabusa2 mission. Construction of the cleanroom was completed in 2018, leaving 2 years for facility testing and

rehearsals. There are currently no plans to move the Hayabusa laboratories to another facility, but more room will be needed for the Martian Moons eXploration (MMX) samples once returned.

Hayabusa2 samples are expected to arrive back to Earth in December 2020. It should be noted that construction was completed 2–3 years before samples arrive back to Earth for each sample return mission. This provides ample time to allow the cleanroom lab to outgas (which takes around 2 years as per JSC's Organic Contamination Baseline Study) and develop operational procedures for handling samples.

Summary

The curation offices at JAXA and NASA have developed a strong working relationship over the past 15 years. The organizations not only share samples (e.g., Hayabusa, Hayabusa2, OSIRIS-REx, MMX), they actively collaborate to develop technology and troubleshoot problems. While the CCs that JAXA developed for both Hayabusa missions are highly customized to meet the needs of their respective missions, the impressive designs serve as an example of prioritizing sample safety (e.g., vacuum, pure dry nitrogen, controlled/limited materials) while keeping the cost down.

Resources

McCubbin et al. (2019) Advanced Curation of Astromaterials for Planetary Science https://doi.org/10.1007/s11214-019-0615-9

Yada et al. (2014) Hayabusa-returned sample curation in the Planetary Material Sample Curation Facility of JAXA. https://doi.org/10.1111/maps.12027

Calaway, M.J., C.C. Allen, and J.H. Allton (2014) Organic Contamination Baseline Study in NASA Johnson Space Center Astromaterials Curation Laboratories, NASA TP-2014-217393, July 1, pp. 108.

Institute of Space and Astronautical Science – Sagamihara Campus http://www.isas.jaxa.jp/en/about/facilities/sagamihara.html

Hayabusa Project: Lid-opening Mechanism to Remove the Sample Catcher – Hitachi https://www.youtube.com/watch?v=5hUhwDlWYSk&list=PLqRcNDnojP49m413seOD5_g4p94dqReKQ&index=4

Hayabusa Project: How to Collect Samples from the Sample Catcher – Hitachi https://www.youtube.com/watch?v=Ld1EUIay3Ms&list=PLqRcNDnojP49m413seOD5_g4p94dqReKQ&index=5

Hayabusa Project: State-of-the-art technologies for clean chamber – Hitachi https://www.youtube.com/watch?v=oGtvBKDnCx8&list=PLqRcNDnojP49m413seOD5_g4p94dqReKQ&index=6

JAXA Presentation to JPL/JSC. 20190829MSRteamIntro

2.2 Thales Alenia Space, Italy (TAS-I): Turin, Italy

Reason and Justification for Visit

Thales Alenia Space in Turin, Italy used an ultraclean and sterile ISO 3 / airborne molecular contamination 9 (AMC-9) isolator line to clean and assemble the most critical hardware for ESA's ExoMars Mars Lander System. MSR isolator lines may require this level of cleanliness and sterility in a future receiving and curation facility.

Facility Description

TAS-I has been a prime contractor for ESA and other aerospace/defense sectors for the design, development, and production of spacecraft and associated hardware for both robotic and human spaceflight since 1988. For ESA's ExoMars program, TAS-I is the prime contractor for the development of the European mission elements as well as for the Spacecraft Composite (SCC) requirements and design for ExoMars 2016 and ExoMars 2020 (now launching in 2022). ExoMars 2020 lander and rover scientific mission objectives are to search for signatures of extant or extinct life, characterize the surface environment, and characterize the water/subsurface environment between 0 to 2 m in depth. ExoMars 2020 is designated Committee on Space Research (COSPAR) Category IVb, and the project must comply with ESA planetary protection requirements document EXM-M2-RSD-ESA-00002. Consequently, the launcher upper stage probably of impact must be ≤ 1×10^{-4} for 50 years after launch and the spacecraft probability of impact ≤ 1×10^{-2}.

ExoMars 2020 mission planetary protection bioburden bacteria spores' requirements:

- Spacecraft ≤ 500,000 Total Bacteria Spores
- Descent module ≤ 460,000 Total Bacteria Spores and ≤ 270,000 Surface Bacterial Spores
- Carrier Module ≤ 40,000 Total Bacteria Spores
- Rover module ≤ 20,000 Surface Bacteria Spores

Average surface bioburden density on the rover and descent module was ≤ 300 bacterial spores/m^2 on exposed internal and external surfaces and average surface bioburden of the rover life detection subsystem was ≤ 0.03 bacterial spores/m^2 .

Following this requirement, Table 2.2-1 provides the maximum terrestrial organic contamination for life detection.

Table 2.2-1. Maximum terrestrial organic contamination for life detection.

Substance Class	Contamination Level per Gram of Martian Sample Delivered for Life Detection
Material from biological sources	$\leq 50 * 10^{-9}$ gram
Monomers of Kapton, Mylar, and PTFE	$\leq 500 * 10^{-9}$ gram
Fluorinated technical lubricants	$\leq 500 * 10^{-9}$ gram
Any other organic compound	$\leq 50 * 10^{-9}$ gram

Source: TAS-I

For ESA PP, the bioburden assays were conducted per EXM-M2-PRD-AI-0162 (ECSS-Q-ST-70-55C tailored for ExoMars).

In order to meet the stringent organic and bioburden requirements, TAS-I approached Comecer to design and construct a glovebox/isolator to meet the hardware precision cleaning and assembly requirements for the life detection mission hardware.

Containment Methods

TAS-I has an existing large ISO Class 8 spacecraft assembly high-bay. Inside an approximately 5,000 ft^2 section of this high-bay, TAS-I constructed an ISO Class 7 bioburden-controlled cleanroom (approx. 2500 ft^2) to house a clean isolator glovebox for precision cleaning and assembly. HVAC was directly ducted to the fan filter units (HEPA and charcoal filtered). All flight hardware assembly was ISO Class 8 or better, ISO Class 7 with bioburden-controlled cleanroom for critical assemblies, and ISO Class 3 with AMC controlled for select organics for life detection subsystems.

Comecer conducted a research and development study and designed an ultraclean multi-chamber isolator that could provide a sterile and AMC-9 < 1 part per trillion (ppt) environment inside the isolator. The isolator was composed of four main glovebox chambers mated together at a length of 7 m long. The isolator was designed as a positive-pressure (+150 to 75 Pa) environment compared with the room pressure with one-pass air ducted by a HVAC system (no inert environment was used). For positive-pressure air, ISO Class 8 cleanroom air from their high-bay was ducted to a large HVAC blower system and conditioned for temperature and humidity. The air was then sent to a large 3-ton active carbon filtration unit built by Camfil to reduce the organic carbon load (or AMC load) with a flow of 5,000 m^3/hour. Air was then pushed through the HVAC HEPA 14 filter and sent to a plenum above the isolator glovebox. The air was then filtered through an ultra-low particulate air (ULPA) 16 filter to create a 0.2–0.3 m/s unidirectional airflow to the work surface that was elevated approximately 10–12 inches above the base of the

glovebox chamber. A second blower was used to take the air at the bottom of the glovebox chamber through the back-bottom of this chamber and exhaust it to outside air.

Glovebox/isolator materials were specially chosen for low outgassing characteristics. Mirror polished stainless steel 316, ethylene propylene diene monomer (EPDM) rubber gaskets, and chlorosulfonated polyethylene (CSM) gloves were used in the construction. TAS-I also added an ISO Class 5 clean tent for hardware transfers into the first chamber. The glovebox had real-time/remote monitoring of the isolator pressure, temperature, and humidity, along with certain valves and airflows. All windows used inflatable gaskets and were able to easily open to allow for cleaning and maintenance. The third chamber also has a window in the back to accommodate a computer screen to view assembly procedures. Although each chamber was fitted with bulkhead doors for isolation, there were no airlocks between the isolator chambers.

Glovebox monitoring of airborne contamination:

- Automated particle counter to assure ISO Class 3 environment
- Molecular organic: Tenax adsorbent tube for AMC-control by thermal desorption–gas chromatography–mass spectrometer (TD-GC-MS)
- Biological air sampler: Manual counter with Air sampler gel-AWEL and Laser-Induced Fluorescent Emission systems for real-time microbiologic monitoring

Glovebox monitoring of surface contamination:

- Particle count witness plate
- Molecular organic witness plate by TD-GC-MS
- Biological fall-out plate

Flight hardware process monitoring of contamination:

- Particle count witness plate
- Molecular organic witness plate by TD-GC-MS

Figure 2.2-1. Glovebox/isolator line at TAS-I. *[Source: TAS-I]*

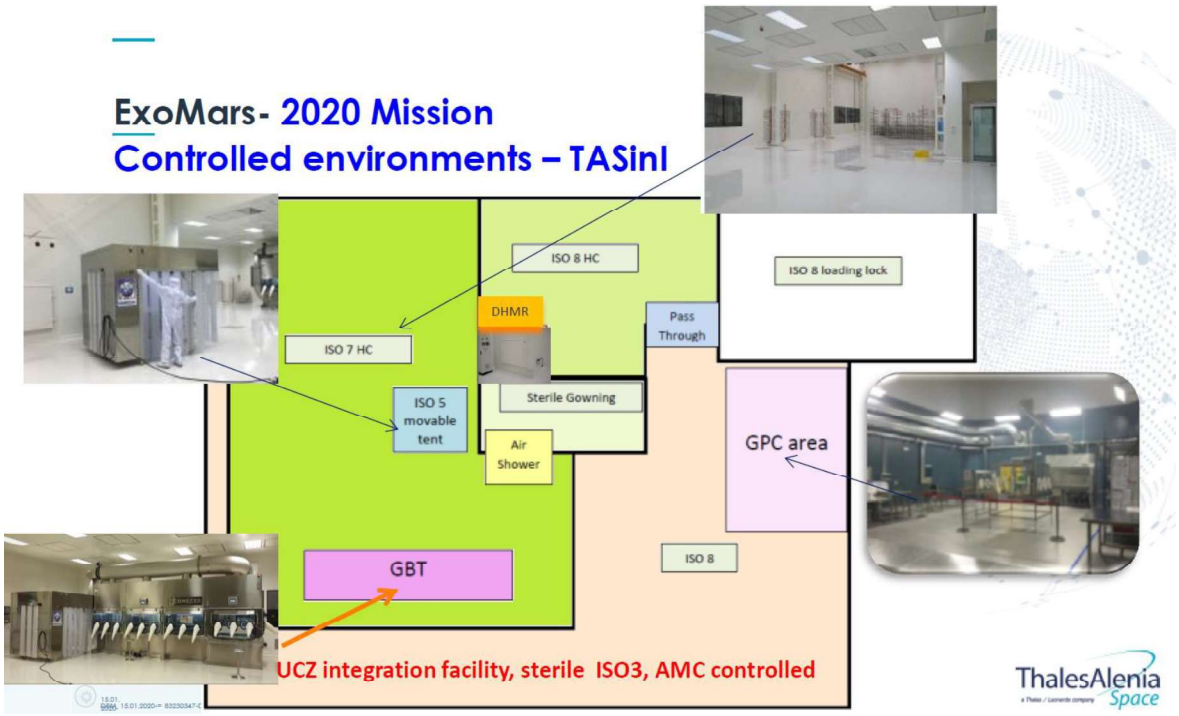

Figure 2.2-2. Cleanroom floor plan at TAS-I. *[Source: TAS-I]*

Cleaning and Sterilization Techniques

Cleaning and sterilization of the main chamber of the glovebox used isopropyl alcohol (IPA) wipes and an integrated bio-decontamination system using the purest hydrogen peroxide solution to achieve a 6-log decrease in contamination.

Table 2.2-2. ExoMars 2020 mission sterilization process.

Bioburden Reduction Process	Followed by European Industries and Agency	Followed by LAV
DHMR	ECSS-Q-ST-70-57C	ECSS-Q-ST-70-57C
Hydrogen Peroxide	ECSS-Q-ST-70-56C	N/A
UV Radiation	N/A	LAV Procedures
Gamma Radiation	N/A	LAV Procedures

All the flight hardware to be sterilized has to be **compatible** with the selected sterilization process.
ECSS-Q-ST-70-53C used to evaluate material and hardware compatibility with bioburden reduction procedures.
Source: TAS-I

Critical flight hardware parts were disassembled, cleaned with multisolvent ultrasonic baths, and packaged in an ISO Class 5 clean tent / flow bench. Most of the flight hardware was sterilized by a dry heat microbial reduction (DHMR) process to achieve 0.03 bacterial spores/m^2. Afterward, the hardware was transported to the glovebox airlock in a sterile ISO Class 5 clean tent keeping sterilization. Inside the glovebox, hardware was further cleaned by a custom-engineered supercritical fluid CO_2 snow cleaning system and then assembled in final configuration inside the final two chambers. This CO_2 snow cleaning was in the second chamber and used a custom fixed nozzle for cleaning.

The Hypalon (CSM) gloves were cleaned and sterilized using IPA 70/30 solution and baked-out at 80°C for 16 hours in ambient cleanroom air. The TAS-I group also noted that the glove samples were cleaned with IPA, thermally pretreated, and then analyzed (volatile organic compounds [VOCs] and tetramethylammonium hydroxide [TMAH]). After being cleaned with IPA, a group of samples were thermally treated at 30°C under an ultrapure air flow for 2 hours and another group of samples at 80°C under an ultrapure air flow for 16 hours. The samples were then outgassed in a microchamber for thermal extraction treated with a chemically inert coating. The sampling was carried out for 3 hours, under an ultrapure air flow, at 30°C. The VOCs were trapped on Tenax TA tubes, and the TMAH was trapped on an ultrapure water bubbler. VOCs were analyzed on an automated thermal desorber / gas chromatograph / mass spectrometer (ATD/GC/MS). TMAH was identified and quantified using ionic chromatography. TAS-I also noted that all the gaskets were cleaned and tested in a similar manner. It was concluded that the 16-hour, dry heat treatment at 80°C reduced the quantity of outgassed VOCs, and the thermal treatment reduced the siloxanes concentrations by more than 90%. The TMAH was undetected.

Gowning to go into the cleanroom:

- Walk through an anteroom into the ISO Class 8 gowning room.
- ISO Class 8 gowning room: Remove street cloths down to underwear and don sterile blouse and trousers, hair net, double overshoes, and gloves.
- Walk through ISO Class 8 high-bay to ISO Class 7 cleanroom.
- Enter ISO Class 7 gowning room: Don sterile gloves and face mask, and then don bunny suit (enter through the back and hood attached). A crossover bench is utilized to then don sterile boots.
- Enter the main ISO Class 7 cleanroom through an air shower and don a second pair of sterile gloves.

Instrumentation/Robotics/Unique Features

N/A

Lessons Learned

N/A

Cost, Schedule, and Lifespan

- 2 years to develop and 1 year for manufacturing
- Glovebox cost approximately: €2.5M
- Integrated CO_2 snow cleaner: €0.5M
- Cleanroom into shell ISO Class 8 high-bay: approx. €1.5M

Summary

To date, TAS-I has the most advanced state-of-the-art precision cleaning, sterilization, and assembly glovebox isolators ever developed for spacecraft hardware. A future MSR receiving and curation facility would benefit from ExoMars missions' experience and their clean sterile assembly processes and procedures.

Resources

Presentation to JPL/JSC."TAS-I 2020 01 15 Margheritis-visita NASA JPL ESA
Glove Bakeout communication (email from Margheritis Diana 3-24-2020)

2.3 Comecer (Headquarters and Manufacturing Facility): Castel Bolognese, Italy

Reason and Justification for Visit

Comecer was the manufacturer of the ultraclean and sterile ISO 3/AMC-9 isolator line that TAS-I used to clean and assemble the most critical hardware for ESA's ExoMars Mars Lander System. Isolator lines for handling Mars samples may require this level of cleanliness and sterility in a future receiving and curation facility.

Facility Description

Comecer was founded in the 1970s as a supplier for the Italian Nuclear Agency and other nuclear development projects in Italy. Since the 2000s, Comecer has become one of the leading manufacturers of shielded cells for the nuclear medicine industry and glovebox isolators for the pharmaceutical industry. In addition, the company has completed numerous isolator and glovebox projects involving primary pharmaceutical production, advanced therapy medicinal products, fill finish manufacturing, laboratory and hospital pharmacy, aseptic food processing, aerospace, and semiconductor manufacturing. Today, Comecer is a subsidiary of the multinational Canadian company ATS Automation Tooling Systems Inc., an industry leader in automation solutions. This provides Comecer with increased expertise with automation within isolators and gloveboxes. Comecer has forged long-term relationships with Denso Robotics and Staubli Robotics, two of the world's leading manufacturers of robotic arms, and routinely integrates their robotic arms and other automation into isolators and gloveboxes. Comecer is one of the few isolator and glovebox manufacturers in the world that develops turnkey systems that involve the integration of high cleanliness/sterile containment with full automation.

Containment Methods

Comecer creates custom isolator/glovebox designs and manufactures their products all in-house. For designs, a team of engineers develops original concepts and subsequently develops 3D CAD models. Afterward, low-fidelity full-size mock-ups are created to test function and space requirements before final designs are released to manufacturing. For manufacturing, raw materials (metals, glass, and plastics) are delivered directly to the facility, where products are machined, fabricated, and assembled; automation, remote monitoring, and/or other specialty systems are integrated; and then completed products are tested and delivered to the customer. Since there are almost no outsources and everything is done at this facility, design to product testing is fluid. The company has experience with the following containment methods:

- Radiation shielding for high-radiation and low-radiation applications
- BSC-I, -II, and -III containment (i.e., BSL-4 rated experience)

- Inert atmospheres (nitrogen and argon)
- Positive- or negative-pressure environments

The primary construction materials for isolator/glovebox enclosures are stainless steel with glass or polycarbonate windows, and low outgassing and/or inflatable gaskets. Stainless steel grade is typically 304L or 316L with mechanical polishing from brushed #4 to greater than #8 mirror finish on planar surfaces. Comecer traditionally does not recommend electropolishing stainless steel on their enclosures, but have accommodated customers in the past if required. For electropolishing, all items would be required to be subcontracted to a third party. For gaskets, Teflon (PTFE), EPDM, CSM, nitrile, silicone, and Viton have been used depending on outgassing limits and engineering structural requirements. For Comecer, inflatable gaskets are common and used for pass-through doors and hinged large front windows that open for access to the main chamber for easy cleaning, maintenance, and process access. The window edge looked to be a router cove cut with a "D" shape grove to allow the inflatable gasket to fill the space when inflated. Glovebox gloves used for pharmaceutical isolators are typically Hypalon (CSM) or nitrile. Comecer has determined through testing that Hypalon products are the lowest outgassing COTS glove on the market. The construction of their nuclear isolators use similar stainless steel enclosures but are lined with 2- to 4-inch-thick lead bricks, as well as the use of lead-lined gloves and windows.

For their pharmaceutical and semiconductor isolators, Comecer has produced isolators/gloveboxes that can meet ISO Class 8 to ISO Class 1 particulate load for ultraclean environments, as well as low AMC environments (AMC-9; < 1 ppt). In order to reduce molecular contamination, Comecer uses a systems engineering approach to track and mitigate contamination. First, they conduct site sampling and quantify incoming contaminates (e.g., outdoor air, lab air, and other products) at specific times using different analytical techniques. Second, they sample and quantify all outgassing material used in the production of the isolator. And third, they identify procedures and quantify chemicals/contaminates during system operations inside and outside of the isolator. The results from these three steps are used to formulate a design and contamination reduction plan. Contamination mitigation could be filtering outside air, changing construction materials to lower outgassing, changing cleaning protocols, and/or developing operational procedures that would also reduce AMC. AMC validation and outgassing characteristics are typically done by TD-GC-MS of an exposed Tenax adsorbent tube.

Most of their ultraclean environments use single-pass air for total extraction/evacuation of generated contaminates and maintain a positive-pressure environment. For a typical system, cleanroom air is taken and pushed through an AMC filter (e.g., charcoal filter for organics), then passed through a HEPA 14 filter. After the HEPA filter, the air is blown into a plenum at the top of the isolator/glovebox (Figure 2.3-1). The air is then forced through an ULPA 16 filter to create

a unidirectional (laminar) airflow to the product processing height, which is 6 to 12 inches from the bottom of the isolator/glovebox. Afterward, the air is exhausted from the back-bottom of the isolator/glovebox and delivered to outside of the cleanroom. The airflow is usually 0.2 to 0.3 m/s on the work area and is not necessarily at 0.45 m/s to good manufacturing practice (GMP) standards. Note that for the ExoMars project, 3 tons of active carbon was used for the AMC filtration with a flow of 5,000 m^3/hour. This method created the ISO Class 3 environment for particulates and the AMC-9, < 1 ppt for contaminates. Comecer has used similar methods for inert atmospheric environment by filtering, directing gas flow, and choosing low-outgassing materials carefully.

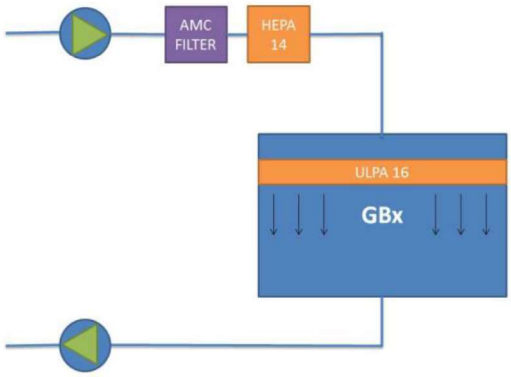

Figure 2.3-1. Diagram of the air flow for the ExoMars isolator. *[Source: Comecer]*

Cleaning and Sterilization Techniques

Comecer did not go into the details on cleaning methodologies and seem to rely on customers for details on cleaning methodologies. However, they have experience with typical sterilization techniques required for the medical and pharmaceutical industry and have built gloveboxes with integrated VHP cleaning system as well as integrated autoclaves. Comecer does not use cleanrooms for assembly of their products. For the most part, isolators and gloveboxes are gross cleaned and assembled. Afterward, IPA wipes are used and then the product is delivered to the customer. Comecer does not have any precision cleaning capabilities. However, seem willing to work with customers and open to more stringent manufacturing techniques.

Instrumentation/Robotics/Unique Features

Comecer has the in-house capabilities for full automation of their isolators/gloveboxes. All gloveboxes seem to have routine monitoring of air/gas flow, differential pressures, temperatures, relative humidity, particle counter, and other automated functions such as doors and transfer ports. All of these sensors interface with a central built-in flat-screen control display that can be remotely controlled and monitored. Comecer has experience with fully automated valves and pass-through chamber doors, has demonstrated capabilities with the integration of

rapid transfer ports (RTPs), and has custom designs for rapid transfer isolators used for live animal exchanges.

The most impressive capability was their integration of robotic arms produced by Denso Robotics and Staubli Robotics into their pharmaceutical product lines. These highly polished stainless steel robotic arms were fully sealed and cleanable. These isolators had no glove ports and could process products remotely through a series of six to eight chambers without the need for human intervention via gloves. Comecer also showed that they commonly use wobble sticks for their nuclear gloveboxes to move samples through their pass-throughs.

Lessons Learned

N/A

Cost, Schedule, and Lifespan

Comecer was asked about hypothetical costs and schedule for the production of a double-walled isolator. A complex project usually takes 1 to 2 years of design before fabrication begins. Dependent on the complexity of the design, it would take 1–3 years for production of an isolator. The cost would again depend on design, but could be anywhere from $2M to $10M+.

Summary

Comecer seemed to be well suited to potentially design and manufacturer isolators required for MSR receiving and curation facilities. Comecer has many unique manufacturing experiences and a proven record of complex designs for low-outgassing clean/sterile isolators coupled with integration of robotics. The manufacturing facility also seemed to be able to handle large orders of complex isolator designs. Our team has not come across another isolator manufacturer that has all of these combined traits under one roof.

Resources

https://www.comecer.com/**2018-video-highlights/**
Presentation to JPL/JSC “AMC_Filtration_EN_NT”

2.4 Airbus Defence and Space: Stevenage, UK

Reason and Justification for Visit

Airbus Defence and Space in Stevenage features their Bio-Clean Facility (BCF) for hardware preparation for planetary lander missions. This highly controlled environment is similar to the type of environment that may be implemented to support the stringent cleanliness requirements for contamination control in an MSR SRF.

Facility Description

For over six decades, Airbus Defence and Space in Stevenage in Hertfordshire has been the lynchpin for the development and construction of telecommunications, scientific, earth observation and meteorology satellites, planetary surface robotics, spacecraft structures, propulsion systems, mechanisms, and antennas. The assembly, integration, and test (AIT) facilities offer a comprehensive suite of manufacturing and test capabilities from piece part manufacture, construction of light-weight honeycomb panel composites, and carbon fiber–reinforced polymer (CFRP) filament wound composites to full structure assembly, including propulsion, harness and thermal subsystems, to the AIT of complex satellites in ISO 8 cleanrooms. The latest addition is the BCF where the ExoMars rover vehicle was built for the 2020 mission to Mars.

The BCF in Stevenage was designed for ISO Class 8 “highly controlled” cleanroom with bioburden control in mind; although the BCF typically operates at an ISO Class 7 HC since commissioning, with control and monitoring per ECSS-Q-ST-70-58. The facility is uniquely built with all stainless steel walls and ceiling for increased contamination control for organics and bioburden. The floors are made of polyurethane resin with bacteria anti-proliferation technology. The facility has a pre-change anteroom, change room, air shower, and a connecting hallway to enter the main assembly cleanroom or integrated Microbiology and Cleanliness and Contamination Laboratory. Adjacent to the main assembly cleanroom is a preparation cleanroom with airlock for large hardware. Interlocked double-door transfer hatches are also available between the preparation and main assembly cleanrooms to move small items. The facility also has integrated control room and viewing areas. The BCF was the home on Earth for ESA’s ExoMars rover vehicle, as all the integration activities including payloads and instruments were performed at the BCF. The BCF was designed and built by a multifunctional team with different areas of expertise, including planetary protection. The facility was audited as part of the commissioning activities by ESA. The facility is suitable for all space missions requiring bio-clean AIT.

Figure 2.4-1. AIT room of the BCF in Stevenage, UK. *[Source: Airbus]*

Figure 2.4-2. Engineer working in AIT room of the BCF in Stevenage, UK. *[Source: Airbus]*

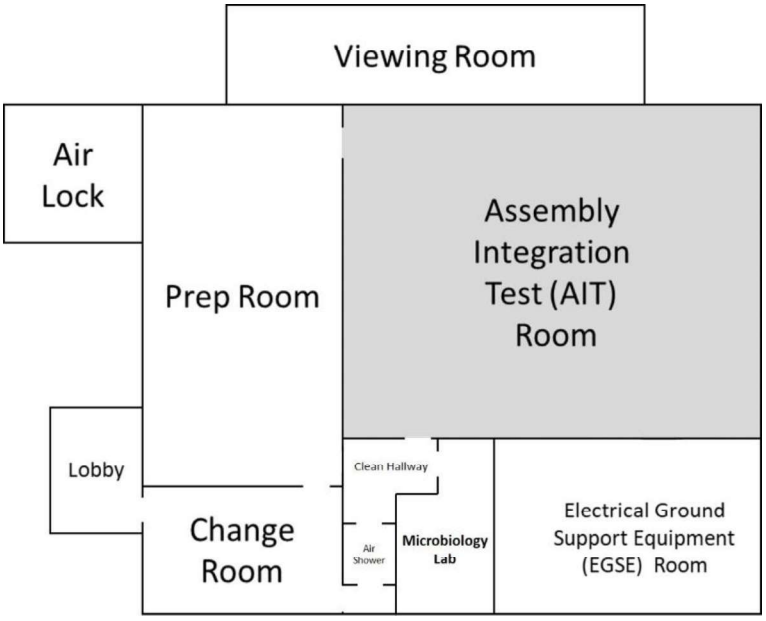

Figure 2.4-3. Floor plan of the BCF in Stevenage, UK.
[Source: Adapted from RAMA personal notes]

Containment Methods

The BCF is not a biological containment facility.

Cleaning and Sterilization Techniques

Material Compatibility

The BCF is a standalone facility. Nominally rated at an ISO Class 8, BCF is operated as an ISO Class 7, but is potentially much cleaner at ISO Class 5 when active. A schematic of the layout is pictured in Figure 2.4-3. Ensuring that construction materials were compatible with the overall cleanliness of the facility, several technical trades and options were investigated. The vetting included materials not in BCF rooms, but nevertheless in contact with the air supply (e.g., ducting, filter housings, duct sealants). Reducing the overall VOC emissions is critical to maintaining the ISO cleanliness necessary for ExoMars. This level was maintained at <5g/liter of organics. Built-in VOC sensors were also available in the early integration phases for this purpose. There was no electroplated finishing on the stainless steel (i.e., zinc galvanizing), which helped produce a non-shedding surface commonly seen with nickel.

ExoMars Vault

To maintain the cleanliness of the BCF, 4–6 people maximum would be allowed to be active at one time. Each room had a 15 Pa pressure cascade with a non-laminar floor. Since it is a large

area to control, organics (microbes) collected in "dirty" areas were routinely assayed. The use of regional laminar flow areas was used where needed. Electrical ground support equipment cables run under the floor through sealed conduits to central hubs located inside the main bio-clean area. The exposed cable ends are then wrapped with Kapton tape to improve cleanliness measures and avoid cross (molecular) contamination by contact.

Commissioning for Microbial Cleanliness

Documents:

- EU GMP Annex 1: Manufacture of Sterile Medicinal Products—revision November 2017
- ECSS-Q-ST-70-55C: Microbial examination of flight hardware and cleanrooms

Procedures:

- Assays: Daily wipes and swabs are collected, followed by ATP or MALDI-TOF analysis.
- Bake-out of facility: Heat vents are turned on while the facility is at rest, and limited number of people are allowed into rooms for 200 days before use.
- Filters: Carbon filters are changed after 9 months and again at 6 months before use.
- Cleaning solutions: Three different agents are used during commissioning and throughout the BCF lifecycle. Agent 1 is used for 4 weeks, followed by Agent 2, and maybe Agent 3 as needed.
  - Agent 1: Quaternary ammonium compounds
  - Agent 2: Lauramine N-dodecyl (dodecyldimethylamine oxide)
  - Agent 3: Pentapotassium

Instrumentation/Robotics/Unique Features

The BCF used stainless steel laptops in the AIT room along with other novel ground support equipment to maintain cleanliness. No robotics are currently installed or planned for use.

Lessons Learned

Custom cleaning agents were used to reduce the bioburden. During experimentation, incorrect cleaning could etch some of the stainless steel walls. Therefore, cleanroom construction materials should be matched with appropriate cleaning agents.

Cost, Schedule, and Lifespan

The timeline for implementation of the BCF took approximately 1.7 years, which included the facility bake-out, cleaning, installation of broad-spectrum carbon filters upstream of HEPA filters (intake and recirculation air), and a daily biological assay monitoring.

Summary

The Airbus Defence and Space BCF in Stevenage is an impressive building that meets all expectations for microbial cleanliness and contamination control. Its highly regulated construction, commissioning standards, and operations make this facility a standout across any cleanroom to date. Given the potential unique and stringent requirements that would be in place for the MSR SRF, the Airbus BCF serves as an appropriate model for understanding how stainless steel could be used to provide an ultraclean environment. As we understand more about the BCF cleanliness model, combined with other facilities that demonstrate the effectiveness of stainless steel for high-containment labs, appropriate decisions can be made to develop effective requirements for an MSR SRF.

Resources

None.

3 ESA Technology Facilities

3.1 Remote Manipulation (RM): Thales Alenia Space, UK (TAS-UK) and University of Bristol Robotics Laboratory, Bristol, UK

Reason and Justification for Visit

TAS-UK, under contract to ESA, has developed a remote manipulation breadboard that could be used in a double-walled isolator (DWI) (also developed by TAS-UK with University of Leicester, under contract to ESA). Due to the possible integration of this robotic system into the DWI, this could be an important contribution from ESA for a notional MSR SRF, and as such, it is important to understand the work being done and interact with the team. Representatives from TAS-UK, University of Bristol, UK Space Agency, and ESA were in attendance. The visit was extended to the University Bristol Robotics Lab, which has been working in collaboration with TAS-UK.

Breadboard Description

The breadboard consists of a mockup of the DWI space, with a Kuka LBR IIWA R800 robotic arm (about the size of a human arm), a two-finger gripper with a force/torque sensor, and a haptic controller (Force Dimension Sigma 7) tied to a workstation. Interconnection between the workstation and manipulation hardware is via ethernet, the kind of interface that would allow remote access.

Instrumentation/Robotics/Unique Features

Software and models have been developed for constraints on the arm access (perimeter of the DWI and internal objects), arm and gripper positioning, and contact sensing of the object being manipulated.

The basic operating system is open-source Robotics Operating System (ROS), a standard framework for robotic systems. Their software allows point-to-point transitions to be performed automatically and haptic operations to be performed in local task space. Software simulating the working environment allows planning, safe operation, the development of control algorithms, and operator training.

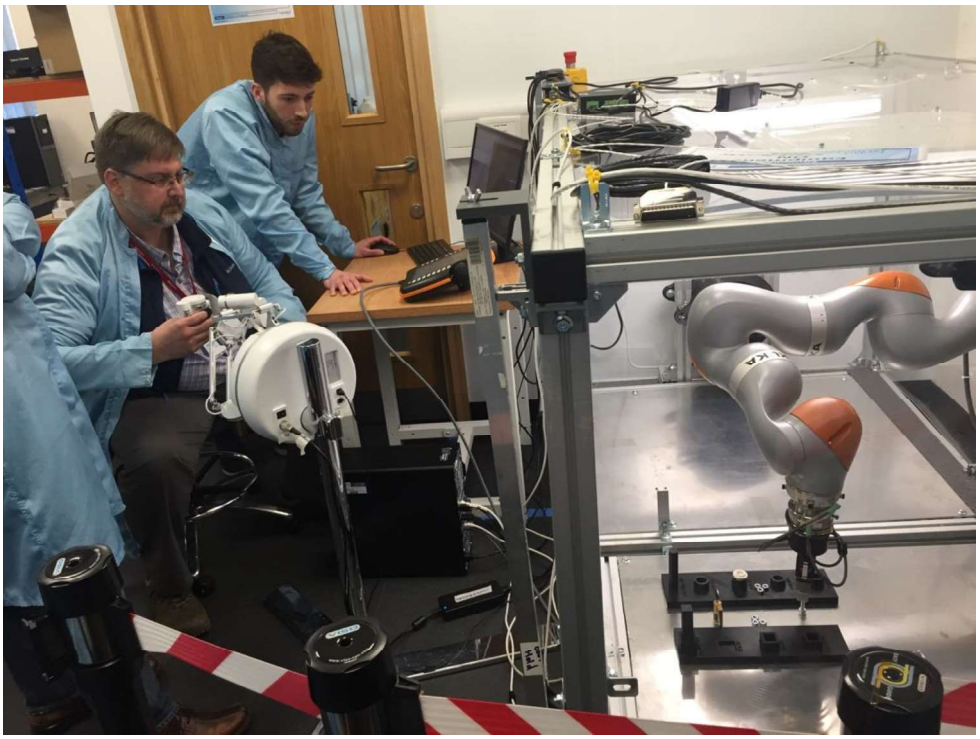

Figure 3.1-1. One of our team members using the breadboard to screw a nut onto a bolt. *[Source: TAS-UK]*

Development has included performing basic tasks like putting a key in a lock and screwing a nut on a bolt. It also has been used to reach into a cylinder analogous to a RTP to remove a sample tube. Haptic feedback has been incorporated and was demonstrated to the NASA team.

The next steps are to perform scientific tasks related to tube manipulation and sample extraction.

This first phase of the testbed development task is complete, and it is being transferred to a facility in Harwell to be experimented with by a sample scientist of ESA and roboticists.

TAS-UK indicated that they also have a micromanipulator with tweezers that they are experimenting with in conjunction with a microscope. It is already in Harwell.

Lessons Learned

TAS has a lot of experience with arms that operate in space and test arms that operate in 1g, which can be capitalized on.

In developing robotics for sample and tube manipulation, one of the challenging aspects is working safely within the space constraints of the isolator.

Cost, Schedule, and Lifespan

Funding for a next phase has not been allocated as of the time of this visit. The next phase may include looking at alternate operating systems; most have ROS packages, which is a rapid prototyping environment.

Eventually, they will be working on manipulation with no line-of-sight, using cameras.

TAS has developed a comprehensive plan for steps forward, but funding is uncertain. Current funding will end with the delivery of the testbed to Harwell, which is expected by the time of this report.

University of Bristol Robotics Research

Our team was taken to the Robotics Lab at the University of Bristol, which is associated with the task at TAS. An amazing variety of work is being done in the lab as can be seen at https://www.bristolroboticslab.com/. There were two research activities that were of particular interest that could benefit MSR robotic manipulation.

1. Haptics for Tele-Surgery
   This research is looking at haptic feedback on DaVinci surgery end effectors and gloves. This could assist in more effective control of delicate operations.
2. TacTip

   This is a soft plastic or rubber sensing surface that has a matrix of white-tipped pins on the back side that is imaged with a miniature camera. Subtle deformation of the plastic

tip changes the matrix and, through optical processing, a soft touch to actuation can be achieved (Figure 3.1-2).

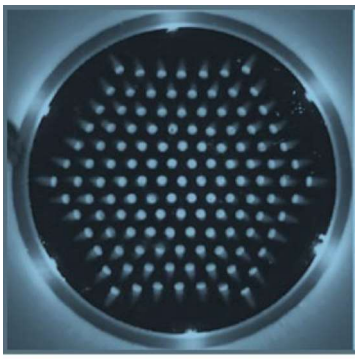

Figure 3.1-2. Backside of sensing surface with white-tipped pins. *[Source: University of Bristol]*

Summary

The RM task is focused on a robotic solution in the context of ESA's DWI concept. It is a functioning testbed designed to examine working within the confines and workspace of a DWI mockup. The testbed will soon be moved to a facility in Harwell for further testing by a sample scientist. The software platform is a common robotics operating system, which could allow for broader contributions. TAS is working with the University of Bristol Robotics Lab, which is doing some unique research in small haptic manipulators that could eventually be applicable to handling hardware and samples.

Resources

NASA ESA visit to Remote Manipulation Breadboard (11th February 2020)

Description of ESA RM System Breadboard foreseen to be used in the Mars Sample Receiving Facility (SRF); https://www.hou.usra.edu/meetings/marssamplereturn2018/eposter/6010.pdf

Univ of Bristol Haptic Research; http://www.brl.ac.uk/research/researchthemes/medicalrobotics/hapticsfortele-surgery.aspx

Univ of Bristol TacTip Research; http://www.brl.ac.uk/research/researchthemes/medicalrobotics/tactip.aspx

Ward-Cherrier, Benjamin & Pestell, Nicholas & Cramphorn, Luke & Winstone, Benjamin & Giannaccini, Maria & Rossiter, Jonathan & Lepora, Nathan. (2018). The TacTip Family: Soft Optical Tactile Sensors with 3D-Printed Biomimetic Morphologies. Soft Robotics. 5. 10.1089/soro.2017.0052. https://www.liebertpub.com/doi/full/10.1089/soro.2017.0052

3.2 Double-Walled Isolator (DWI): University of Leicester, Leicester, UK

Reason and Justification for Visit

The University of Leicester has the breadboard of the DWI that ESA has developed. Since the DWI is a potential contribution from ESA for a notional MSR SRF, it is important to understand the design and take steps to develop a working relationship with the team.

Breadboard Description

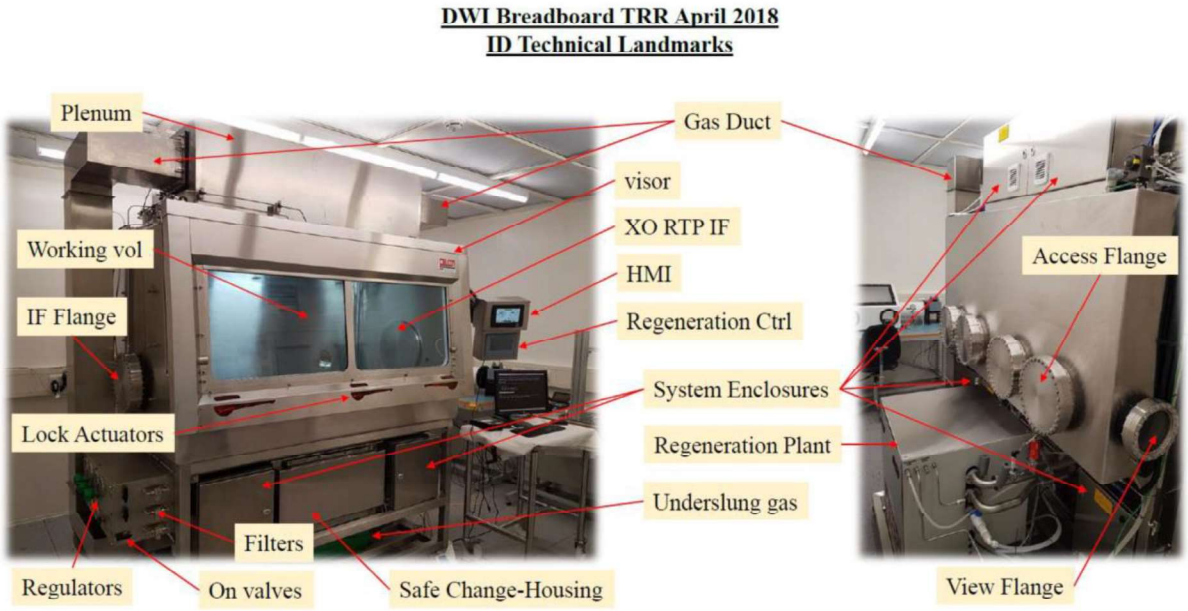

Figure 3.2-1. Double-walled isolator breadboard. *[Source: University of Leicester]*

The DWI was developed under ESA contract to TAS-UK, starting in 2016. The breadboard at the university has been undergoing testing over the past year, demonstrating performance. The purpose of the system is to provide a pristine environment for operation on the samples, and at the same time providing BSC-III isolation.[1] Typically, a pristine environment is provided by a container (glovebox) at positive pressure compared to the outside. Biosafety containment is usually in a container at negative pressure compared to the outside environment. This isolator provides both, with double walls that create an interstitial space as necessary. However, much of this isolator is a single wall— the glass front (visor) and some other areas of stainless steel where there are no penetrations. The areas that have penetration have a double wall with a common interstitial space. While the breadboard does not have double seals as a cost savings, all seals are expected to be double with the inner space connected to the common interstitial volume.

[1] BSL-4 containment can be provided by a BSC-III in a lesser BSL space (not requiring positive-pressure suits) during operations or provide redundant biocontainment in a BSL-4 suit lab.

Figure 3.2-2. Team viewing double-walled isolator (relative size).

Containment Methods

The pressure regime in the current breadboard has positive pressure in the interstitial space. This paradigm allows for keeping the containment on the central space (or working volume), which is at a lower pressure with the Mars material, while simultaneously keeping exterior contamination, which is also at a lower pressure, from reaching the samples. To minimize the amount of gas needed, the gas in the interstitial space is basically static, only requiring a periodic top-off.

The pressure scheme seemed optimal in our discussions. It, however, needs to be verified that it could serve as a BSC-III for primary containment. The breadboard is flexible enough that a different scheme could be used, such as what was thought of in the SRF 2004 designs, which had a negative pressure in the interstitial space. This would create an outer container that is more like a BSC-III, and an inner container that is like a cleanroom. The pressure regimes were shifted to create an overall negative-pressure regime within the isolator to prioritize planetary protection concerns over sample safety, since in the case of a containment breach, the new regime would draw air into the isolator instead of it flowing out.

The inert gas in both the inner container and the interstitial space could be both ultrapure nitrogen (N_2), with a pressure sensor in the intestinal space to detect leaks. Alternatively, the interstitial gas could be different, such as argon (Ar), which could be sensed if it leaked out in either direction.

In the working volume, gas flow is from the top, and there is an operational tray on the bottom, with sides with slots for gas flow to minimize loss of sample. The flow has been shown to be laminar 3 inches above the tray, the recommended height for sample manipulation. Flow can be adjusted to meet the needs of contamination control (removal of contaminates). Flow can be turned to zero for sensitive operations like weighing, but tests will have to be performed to ensure contamination control standards can be maintained.

The gaseous nitrogen (GN_2) is recirculated in the breadboard and cleaned by HEPA and ULPA filters, and a molecular sieve is used to remove O_2 and water. There was a discussion as to whether traditional HEPA filters on the inlet are clean enough, and stainless steel (3 nm) or ceramic filters were suggested as a potential to be investigated in the future. Dual HEPA filters in series are being utilized, so that the first filter (protecting the second filter) can be safely changed often without disturbing the other (which remaining relatively clean, could last for months). There is concern as to whether recirculated gas would be clean enough for MSR. Single-pass GN_2 is typically used in JSC's curation labs; this could be implemented by gas bottles or from a large tank external to the facility, depending on the flow needed and building architecture.

The system is meant to be used with robotics yet gloves or remote manipulators/wobble sticks could be accommodated. However, providing double-walled isolation may be a challenge.

Transfer of samples, tubes, tools, etc. would be accomplished using an RTP. The seal of the RTP can be heated to destroy organics and biologics.

All penetrations are implemented with standard vacuum flanges, modified to have double seals. This implementation simplifies interfaces with the DWI.

316L stainless steel construction is used in the isolator. Currently, silicon seals are used for cost reasons. In the future, Teflon can be used, or at least seals could be Teflon coated. Testing thus far gets particle levels to ISO Class 1, with the cleanroom being at ISO Class 6. Biologics are undetectable with 3M Petrifilm™ techniques, but VOCs are not low enough because of materials used like silicone (for cost reasons). With the proper material selection in the future, it is thought that the VOCs would be controllable.

The DWI is a sealed closed-loop system. Although it is thought to be operable in a relatively dirty environment, an ISO Class 6 cleanroom is recommended for standard operations. Furthermore, an AIT aseptically-managed ISO Class 5 area is necessary to prepare the DWI and transfer materials into it. It may be beneficial to also operate the DWI at ISO Class 5 so that if there is a breach, there would be some cleanliness protection. The DWIs are moveable and can be transferred from room to room (approximately 1,500 kg on casters).

The DWIs can be chained (ported) together or used separately with samples transferred via RTPs.

There is concern that the size of the current breadboard is too tall to fit within some existing BSL-4 facilities, especially if a cleanroom shell is needed as well. There is also concern that facility doors my not be wide enough to transfer intact DWIs. This recognizes that typical BSL-4 facilities are single-pour construction and are not readily modifiable. The unit had to be disassembled to get into its current university lab. The unit is 2.4 m high x 2.4 m wide x 1.4 m deep. It was stated that the form factors can be readily modified in the future to better accommodate restrictions. They are estimating that 0.6 m can be taken off the height.

Further performance testing is to be initiated, as well as the development of a vacuum-compatible instrument accommodation box as an annex to the DWI. They also plan to demonstrate instrument accommodation.

Instrumentation/Robotics/Unique Features

N/A

Lessons Learned

N/A

Cost, Schedule, and Lifespan

Comecer (a capable developer) was asked about the schedule for a hypothetical production for the complexity of a DWI. A complex project usually takes 1 to 2 years of design before fabrication begins. Dependent on the complexity of the design and number of units, it would take 1 to 3 years to produce a set of isolators. ESA estimates that the development cost would be around 20M€, then about 0.6M€ per unit (without contingency or remote manipulators).

Summary

The DWI is a potential solution for providing both a primary pristine sample manipulation/examination environment, as well as primary BSL-4 containment. The current breadboard provides a reasonable approach and has the flexibility to adapt to future constraints and requirements. Future augmentations have been thought about by the technical team, and they are on a path that could contribute to SRF solutions. DWI's potentially could be used for long-term curation, for storage, and even used in an off-site implementation such as examination of samples by a synchrotron or at the landing site. NASA should work with the team to get assurance that the current scheme (implementation and pressure regime) would be certifiable in the United States. The next phase that is about to be initiated includes developing instrument accommodation capabilities; it would be prudent to have some collaboration in exploring instrument accommodation with or without the DWI.

This element should be considered for potential contribution from ESA to an international SRF.

Resources

DOUBLE WALLED ISOLATOR TECHNOLOGY FOR MARS SAMPLE RETURN FACILITIES, https://www.hou.usra.edu/meetings/lpsc2019/pdf/2408.pdf

DWI: Double Walled Isolator, a Potential Solution for MSR & CAT V Sample Handling, https://www.hou.usra.edu/meetings/lpsc2019/eposter/2408.pdf

Presentation to JPL/JSC “DWI Tech Overview Feb 2020 f (redact)”.

J. M. C. Holt, et al., DWI: Double Walled Isolator, a Potential Solution for MSR & CAT V Sample Handling, https://www.hou.usra.edu/meetings/marssamplereturn2018/eposter/6009.pdf

4 Summary Observations and Recommended Follow-up

4.1 Observations (Facility Capabilities and Considerations, Existing Facilities, Programmatic Advice)

Facility Capabilities and Considerations

1. **Sterilization methods differ at various facilities.** This variation is mainly determined by the specific types of pathogens that are being studied at a particular facility. However, BSL-4 facilities have not standardized or specified particular sterilization methods. The majority of BSL-4 facilities do seem to be leaning toward VHP. Sterilization in BSL-4 facilities is done with formaldehyde, chlorine dioxide gas, and VHP. Each of these sterilization techniques could potentially cause different and varying levels of contamination to the samples.

2. **New facility sterilization techniques are continually being investigated.** For example, GNL is developing the capability to use activated ionized hydrogen peroxide (AIHP), which is believed to be more efficient than VHP.

3. **All materials removed from the BSL-4 labs must be autoclaved, chemically inactivated, irradiated, or sealed** in double-walled, airtight containers for transfer outside of biocontainment and submerged in a dunk tank to chemically disinfect the exterior surfaces of the container for storage or transfer to another process.

4. **Facility decontamination methods** currently used in BSL-4 laboratory suites are tested using known terrestrial biological indicators. To determine if these methods are compatible with Martian material in mitigating cross-contamination in a shared existing suite, additional testing is required in collaboration with BSL-4 safety officers.

5. Porton Down and GSU operated their BSC-III cabinet lines without pressurized suits or PAPR PPE. Dependent on the biological risk assessment, it may be conceivable that an **MSR SRF BSC-III cabinet line could be nominally operated in traditional cleanroom garments** with little need for BSL-4 type pressurized suits or PAPR PPE. However, BSL-4 type pressurized suits (air-hose connected or self-contained) may be required when opening the isolators during maintenance or other operations.

6. Porton Down operated their BSC-III cabinet line in an airtight BSL-4 constructed room with pressure-sealed doors and HVAC containment. In contrast, GSU operated their BSC-III cabinet line in a non-airtight constructed room (similar to a BSL-3) without pressure-sealed doors for containment. It should be noted that Porton Down routinely works with human samples isolated from emerging disease outbreaks, which could contain unknown agents (similar to USAMRIID), and GSU is only certified for handling certain known pathogens (e.g. Herpes B virus). Since MSR samples would be considered as unknowns, the Porton Down airtight model could be a better approach for MSR. In addition, operationally, GSU would have to fumigate their cabinet line before opening to the room (for contingencies or planned), which may not

be an option for MSR. However, NASA should investigate the pros and cons of these models (non-airtight vs. airtight secondary containment) further. Redundancy and operational realities should be taken into consideration. *[See follow-up #15.]*

7. **Ultraclean facilities have been implemented for various aerospace projects in the past**. The ExoMars program has implemented probably the most stringent organic and bioburden facility requirements in the world located at Airbus and TAS-I. JAXA Hayabusa and Hayabusa2 missions also have a state-of-the-art ultraclean facility that mitigates inorganic and organic contamination. NASA's Mars 2020 rover and OSIRIS-REx missions have also recently developed capabilities to reduced inorganic, organic, and bioburden in cleanrooms with strict controls. MSR can certainly build upon this knowledge.

8. JAXA, in collaboration with JSC, have developed **state-of-the-art micromanipulation** for small particle astromaterial handling, containment, and transport.

9. **HEPA filtration of exhaust air is universal in BSL-4 facilities**; in the past, USAMRIID used to incinerate the effluent air to sterilize it.

10. **Comecer has state-of-the-art isolator and glovebox capabilities** where robotic and mechanical handling systems are routinely integrated. Comecer may be a candidate for a turnkey end-to-end provider for an MSR robotic sample handling isolator (e.g., the ESA DWI, if implemented). They are very materials conscious, using all Italian 316 stainless steel and developed a proprietary design and process for ultraclean/sterile COTS CSM (Hypalon) gloves for the ExoMars payload cabinet line.

11. **High-purity dry clean air** was used during hardware cleaning and assembly for **ExoMars and Mars 2020**. For astromaterials, JAXA uses vacuum and inert high-purity gaseous nitrogen environments. NASA JSC currently uses single-pass **high-purity gaseous nitrogen** delivered from an ultrahigh-purity liquid nitrogen boil-off. *[See follow-up #12.]*

12. The **ESA DWI breadboard uses recirculated gaseous nitrogen** (derived from purchased ultrahigh-purity nitrogen K-bottle) that passes through a series of gas purifiers and filters before reentering the main isolator chamber. NASA JSC Curation uses single-pass high-purity gaseous nitrogen delivered from an ultrahigh purity liquid nitrogen boil-off for all astromaterial collections. While JAXA maintains pristine Hayabusa samples in vacuum, the samples are processed in isolators that recirculate gaseous nitrogen through a series of purifiers and filters, similar to the DWI system. Using single-pass nitrogen could be a significant functionality problem for an MSR SRF if an existing BSL-4 facility is considered. The DWI design could accommodate either one-pass or recirculation of the gaseous nitrogen. *[See follow-up #12 & 13.]*

13. **Comecer tested a variety of COTS glovebox gloves** and determined that chlorosulphonated polyethylene (CSM or Hypalon) gloves provided the best solution for low organic applications. This is the same result from NASA JSC testing of COTS glovebox gloves conducted in 2001.

14. **Comecer and TAS-I developed a proprietary way to clean COTS CSM gloves for low-organic and low-bioburden use** in the ExoMars payload cleaning and assembly glovebox lines that were thought to be clean enough for their ultraclean hardware cleaning/assembly process. Currently, it has been assumed that gloves would be too dirty and porous for MSR, favoring robotic solutions. *[See follow-up #18.]*

15. The **ESA Robotic Manipulation testbed** could serve as starting point for understanding robotic operations in a DWI, for further development, and other implementations.

16. TAS-I, JAXA, and DWI **all operated their glovebox/isolator in a cleanroom**. These facilities showed that precision cleaning and cleanliness is difficult to achieve. *[See follow-up #21.]*

17. **Mobile and modular high-containment appears to be feasible.** There is risk that no one has done this before for a BSL-4 but utilizing this type of facility could reduce cost and schedule. *[See follow-up #11.]*

18. Germfree and NBAF both suggested that welded **all stainless steel** rooms have many advantages over poured concrete in terms of cost, schedule, pressure testing, and containment certification. *[See follow-up #10.]*

19. In general, the use of **stainless steel for the primary construction material** for cleanrooms and glovebox isolators helps dramatically reduce organic and biological contamination. Stainless steel is also easier to routinely clean during processing. Stainless steel is used in almost every facility that required ultraclean applications.

20. For Hayabusa2, a vacuum environment is preferred for pristine primary containment, and a positive-pressure nitrogen environment is preferred for handling the actual asteroid samples. During Hayabusa, a lesson learned by JAXA was that **handling samples in vacuum became difficult** and were troubled with mechanical problems. This experience was similar to the problems of the high-vacuum complex used by Apollo 11 and 12. *[See follow-up #12.]*

21. **Half-suit systems used at Porton Down** may be something to consider for disassembly of the flight system containment vessels and OS without needing pressurize suits.

22. The **ESA DWI appears to be a potentially valuable part of the SRF solution**, especially with the ESA's remote manipulation pursuit. It needs to be demonstrated that DWI implementation is certifiable as a BSC-III in the United States. *[See follow-ups #9 & 16.]*

23. **Instrument accommodation in BSL-4 and other labs can be challenging** and may be a source of contamination. *[See follow-up #17.]*

24. One of the capabilities in some BSL-4 facilities is tissue digestion and incineration (capabilities for small animals like in Duke-NUS to large-animal capability at NBAF). **Tissue digesters should not be a capability needed by the SRF** (assuming animal studies are not needed or are outsourced).

25. **Effluent waste processing would be needed for an SRF. However, large steam systems** used in major BSL facilities **should not be needed in the SRF.** GSU and Duke-NUS use small chemical and thermal systems. The SRF will most likely not generate a large amount of effluent waste when compared with the larger BSL-4 facilities toured.

Existing Facilities

26. Overall, several U.S. **BSL-4 facilities are world-renowned and have expertise that could be leveraged in building and operating an MSR SRF**. Additionally, since some new BSL-4 facilities may have more capacity for conducting high-containment research and storage, this may represent a potential for MSR for at least some activities (however, the RAMA team purposely did not ask about the feasibility of such an alternative during any of our trips). Of the facilities visited, USAMRIID, NEIDL, GNL, and CDC may be potentials for utilizing space. BSL-4 facility and biohazard expertise could be leveraged from all BSL-4 facilities around the world. *[See follow-up #1 & 2.]*

27. While most BSL-4 laboratories will have the expertise necessary to facilitate meaningful conversations on biohazard testing of Martian samples, it should be noted that **these labs may not be equipped with the proper tools necessary to effectively participate in the MSR biohazard testing process.** Many of these labs are designed for traditional culture-based identification and characterization, coupled with animal testing, which would most likely not be a part of the biohazard cascade testing plan. **Additional steps may be required to augment these labs with equipment suitable for MSR needs, if utilized**. NASA should initiate discussions with the biosafety community and sample science to ensure the proper instrumentation is available or developed to meet the high-containment testing needs. *[See follow-up #7.]*

28. **Existing BSL-4 facilities are inherently not clean environments,** and none that we have visited have been fitted with cleanrooms. BSL-4 facility rooms that house and handle animals and perform necropsies are particularly dirty when compared to a cleanroom environment.

29. Existing BSL-4 facilities use epoxy coating systems on floors, walls, and ceilings. In addition, the air handling systems are HEPA filtered with stainless steel ducting and plumbing. Stainless steel and glass are used throughout the lab for doors and windows. **Many of these materials may be compatible with cleanroom construction practices.**

30. **Significant retrofitting of an existing facility may be required to meet cleanliness requirements.** It is unknown if existing BSL-4 facilities have the cleanliness needed for DWI operations, and if they can be made cleaner for assembly, servicing, and material transfer (suggested by the University of Leicester at aseptically-managed ISO-6 and ISO-5, respectfully). The team explored two possible retrofitting options with BSL-4 experts: (1)

augmenting the air handling system filtration and/or (2) adding a modular cleanroom or clean tent:

(1) Most BSL-4 air-handling systems are already using HEPA filtration, which may or may not be adequate for DWI operations (particle counts have never been taken, but the air flow is at negative pressure, which pushes particle contamination into the lab suites). The team further discussed installing custom ULPA and/or chemical filtration to reduce organics in the air. Unfortunately, existing air handling systems are limited to their original design specifications and may not be able to accommodate the pressure drop with the addition of more filtration as well as increased ducting sizes and runs that are needed for additional chemical filtration.

(2) Retrofitting an existing a BSL-4 room with a cleanroom may be difficult. Typical BSL-4 room heights are around 10 ft. After accounting for breathing air and other utility piping, usable space is limited to around 8 ft. With only 8 ft high usable space, this leaves no room for cleanroom fan filter units and may affect DWI and instrumentation options.

The RAMA team believes this height limitation does not allow adequate space to install a temporary or modular cleanroom and limits options for augmentation of existing air handler systems. *[See follow-up #5.]*

31. If the MSR room(s) are **not properly isolated** in their own lab suite with separate BSL-4 laboratory entrance and exits in an existing facility, there seems to be consensus that the **samples would have to be sterilized before removing them from the facility** to ensure they do not carry terrestrial select agents. Even if MSR rooms in an existing facility are in a dedicated lab suite with no shared spaces, the local facility safety team must still conduct a specific biohazard assessment for MSR activities. The assurance that samples could leave the facility without being sterilized needs to be further explored/clarified with the safety officers of the key facilities visited and the CDC and other regulatory agencies. *[See follow-up #3 & 8.]*

32. Existing BSL-4 rooms typically have some extra future-use plumbing pass-throughs that are currently capped. However, depending on the size needed, **there may be the need for significant retrofitting of concrete walls for added utilities** (e.g., GN_2 piping, cleaning agents, electrical, instruments accommodation). This process could take 2–6 months and require facility approval, taking the lab suite down, X-ray of concrete wall to select drill location, drilling, installation/sealing, conducting pressure decay tests, and facility recertification. Even if the facility allowed this retrofit, the X-ray scans may prove that the reinforced concrete has too many layers of rebar to drill and may have diameter-size limitations. BSL-4 facilities are not typically designed to have future holes drilled through walls. However, external GN_2 may not be needed if recirculation is adequate. *[See observation #11.]* Specific accommodation needs should be defined and addressed with existing facilities. *[See follow-up #6.]*

33. **All toured BSL-4 facilities use a common shared drain piping to their effluent systems between lab rooms, which may be a cross-contamination issue.** Even assuming a separated

BSL-4 lab suite for MSR, an existing facility may require a separate dedicated drain plumbing, piping, and effluent system for MSR activities to mitigate the risk of cross-contamination. However, even if a separate draining system is not required for MSR, there may be additional decontamination methods required (e.g., higher thermal conditions, supplemental chemicals, etc.) to establish a high degree of sterilization confidence of effluents from a common shared system with Martian waste. If needed, this type of retrofit would be difficult and expensive, and existing facilities may not accommodate such a request. *[See observation #31.]*

34. **Square footage floor space is limited in existing BSL-4 facilities with separate entry/exit egresses.** Isolated BSL-4 lab suites are typically < 1,000 ft^2 including all annexed rooms. This leaves little room for DWI sample receiving and processing lines as well as for processing an Earth Entry Vehicle (EEV) and any necessary instrumentation.

35. **Standard APR doors are < 36 inches wide and < 94 inches in height.** This may preclude egress of an MSR EEV container and possible large DWIs as well as other required equipment.

Programmatic Advice

36. The CDC, NEIDL, USAMRIID, GNL, and Porton Down **all emphasized that early and open community engagement is important to gain the public's trust for building a new BSL-4 type facility**. Lack of early public engagement and transparency can lead to a perception of secrecy, mistrust, and misunderstanding. In the U.S., the NEIDL in Boston provided the best lessons learned about the lack of transparency and public engagement, which led to years of public mistrust around the Boston metropolitan area. The result was lengthy litigation, added government regulations, and a new BSL-4 facility that was unusable for a decade (2008 to 2018). Several years after construction was completed and the facility was still not allowed to operate, Boston University changed the NEIDL's leadership and transformation of the lab's culture began (e.g., absolute transparency and active public engagement with increased public tours). A better understanding of BSL-4 operations and the facility's low risk to the public helped foster trust among the community leaders. Early and open community engagement is essential to gain public trust.

37. There is a period between the time when the building is finished and when it is cleared for work on BSL-4 select agents. It could take 1–2 years, and if inspections indicate problems, it could get stretched out for another couple of years. Usually, the work in a facility starts in stages, beginning in BSL-2 and working in pressure suits before it becomes certified to handle select agents. It has been recommended to **engage with regulatory agencies throughout the development process to minimize impacts on the certification period.**

38. **Building construction issues can delay BSL-4 facility opening and commissioning**. As an example, the Boston NEIDL had epoxy wall paint curing problems where paint could not adhere to the concrete, which led to paint flaking issues and containment certification concerns. This problem took more than a year to resolve, and the project missed their completion deadline by 1 year. Ironically, the construction of NASA JSC's Lunar Curation Lab Building 31N had similar epoxy wall paint issues in 1978 that took more than a year to fix and delayed its opening until 1979. There should be enough schedule reserved (at least 1–2 years) to accommodate construction issues, especially with the specialized characteristics of these facilities, and not count on commissioning time to correct them.

39. **Typical lifespan of BSL-4 facilities is about 20 years**, at which time significant renovation may be required.

40. **Locations with increased risk for natural disasters** (e.g., volcanos, earthquakes, hurricanes, tornados, etc.) **require special construction design features** and good operational practices to mitigate risk. NBAF in Kansas required special construction to mitigate F5 tornado risk, and GNL in Texas was constructed to withstand a category 5 hurricane. Both of these facilities also had contingency procedures and operational planning to mitigate against these types of disasters. The UTMB GNL and Shope facilities have already been environmentally tested by successfully surviving a direct eye wall wind impact and storm surge from Category 4 Hurricane Ike in 2008 and massive flooding by Hurricane Harvey in 2017. As a testament to the building's design, no interior damage was reported, and the facility only had minor cosmetic damage to the outside of the building and some basement areas. UTMB/GNL BSL-4 facilities have demonstrated that hurricane-prone areas should not be excluded from consideration, but that the design should account for those stressors.

41. **Lessons learned from NEPA processes at recent BSL-4 construction** sites will be valuable in scoping the NEPA process for an MSR SRF (e.g., USAMRIID, NBAF, and CDC).

42. There are a set of **major collaborative interdisciplinary teams used for the architecture, design, and construction of BSL-4 facilities** (e.g., NBAF). The SRF should use a similar model and capitalize on their BSL-4 expertise.

43. **All the facilities visited have an EIS and risk analyses available**, as well as the NRC and other assessments of their analyses. These are models and contain valuable lessons learned for SRF containment studies. A group should review the sets available and recommend strengths and weaknesses to approaches for the SRF EIS.

4.2 Recommended Follow-Up

1. **There may be potential to implement at least some MSR SRF activities into an existing BSL-4 facility**, if cleanliness and other issues can be overcome. The team purposely did not extensively explore in its visits and follow-up discussion about implications of implementing MSR activities in their facilities. It is recommended that we carry the conversation into understanding a) if there is interest and b) what the ramifications would be. We visited seven (7) of the fourteen (14) BSL-4 facilities in the United States. Eventually, we should consider issuing a request for information to all of them, as well as a couple BSL-3 facilities (e.g., Dugway), that would solicit their input on how they could support MSR SRF activities. *[See observation #26.]*

2. As a follow-up question for 1 above, **what is the potential to attach an MSR SRF to an existing BSL-4 facility and potentially utilize their biohazard expertise**. Could NASA build a brick-and-mortar or modular MSR SRF and attach it to an existing U.S. BSL-4 lab? *[See observation #26.]*

3. Before prospective BSL-4 facilities are investigated for structural compatibility, inquiries should be made about their **anticipated capacity and possible conflicting procedures** that could compromise the Martian samples (e.g., sterilization requirement, shared spaces). *[See observations #31.]*

4. An investigation on possible **structural limitations** of utilizing specific existing facilities should be performed. Some of the necessary information includes, but is not limited to, door sizes (internal and external), room dimensions, shared space (hallways, gowning), and material compatibility. *[See observation #25.]*

5. The RAMA team should further explore the potential of **adapting existing BSL-4 facility room(s) to cleanliness needed.** The investigation could potentially include conducting exploratory particle counts, inorganic fall-out, and organic outgassing tests inside an existing facility. *[See observation #32.]*

6. **SRF accommodation needs** of a facility needs to be defined. *[See observation #30.]*

7. RAMA should continue discussions with existing BSL-4 labs to determine **biohazard testing capabilities** beyond the classical culture-based methods. They should also have discussions with the Committee on Space Research (COSPAR) sponsored SSAP Working Group as to their needs. *[See observation #27.]*

8. For existing facilities, **assurance that samples could leave the facility** without being sterilized needs to be further explored/clarified with the safety officers of the key facilities visited as well as with the CDC and other regulatory agencies. *[See observations #31.]*

9. **DWI development is ongoing at ESA**. Now that NASA has been given the go ahead to study the MSR SRF, we should engage in the development activities since they have the potential to be a central element contributed by ESA to the international SRF. *[See observation #22.]*

10. The RAMA team heard various opinions from the BSL-4 design community on building a containment room out of traditional concrete versus stainless steel or other materials. Further review of the **trades of primary construction materials** for an SRF should be explored. *[See observations #18 & 19.]*

11. **Modular facilities could be a useful concept to reduce costs**. Further understanding the cost and implementation between modular and brick-and-mortar construction would be extremely useful for the MSR SRF. *[See observation #17.]*

12. Further investigation is needed to determine whether **GN_2 recirculation** is a) adequate for MSR science and pristine sample storage/processing and b) a technology that is reasonably achievable in an isolator concept. MSPG should be asked whether vacuum or other gas mediums are needed. *[See observations #11, 12, & 20.]*

13. **HEPA and ULPA filters** are key in containment. There was discussion at the visit on the DWI that these filters may be manufactured in a manner that contains high-VOC materials which may be unacceptable for MSR cleanliness. Appropriate filtering needs further exploration. *[See observation #12.]*

14. The Baker Company (Sanford, ME) developed the BSC-III cabinet line at GSU in Atlanta and the gloveboxes at Boston NEIDL. While the RAMA team visited Germfree and Comecer glovebox manufacturers, it would be good to have an **additional perspective from more U.S. glovebox companies**, possibly ones that have semiconductor and nuclear experience.

15. Evaluate the pros and cons of using a non-airtight **lab (similar to a BSL-3) for secondary containment in conjunction with the DWIs** (this model works for GSU). *[See observation #6.]*

16. The CDC, and any other pertinent agencies, should be consulted as to whether the current **DWI pressure scheme and concept would be certifiable as a BSC-III.** *[See observation #22.]*

17. The RAMA team should look at **a representative set of instruments** that might be used in the SRF, what would be needed to modify COTS instruments for use in the SRF, and how instruments could impact the SRF design, especially if using an existing facility. *[See observation #23.]*

18. There should be a study on whether **gloves could be developed** that can be used in DWIs. The current assumption is that robotics are needed for cleanliness and that a double-walled glove would be difficult to develop. *[See observations #13 & 14.]*

19. **Operational scenarios** need to be developed for disassembly, sample removal and processing, science performed with instruments, and maintenance and cleaning to determine

the regimes of containment and cleanliness required (e.g., pressure suits, scrubs, isolators, etc.).

20. RAMA should **clarify anticipated contamination control requirements** for the SRF with MSPG (or Returned Sample Science group and M2020) and the MSR campaign. *[See observation #16.]*

21. RAMA should further investigate ultraclean **robotics currently used in isolators** in academia and industry.

22. RAMA should gather additional information on **annual operating costs** of the facilities visited.

5 Findings

Facilities and Capabilities

1. **Mobile and modular laboratory** implementation appears feasible and beneficial from a low cost, schedule, and contamination control perspective, even though a BSL-4 has never been implemented before. It should be noted that a modular facility would require an existing large high-bay or require a shell building be built; or a hybrid modality with a new brick-and-mortar building. *[See observation #17.]*
2. **DWIs** (and accompanying remote manipulation) might be **considered for ESA's contribution to an international SRF**. The RAMA team should collaborate with the ESA DWI technology development to assure requirements would be met. *[See observation #22.]*
3. **Remote manipulation and robotics** have not been adequately addressed in the team's visits. ESA demonstrated work they are pursuing, but it is in the preliminary stages. While we witnessed integration of clean robotics inside isolators, the robotic capabilities need to be explored further. *[See observations #15.]*
4. The ESA **ExoMars programs and JAXA had impressive facilities** that implemented **reduced organics and bioburden** in their cleanrooms, isolators, and associated equipment. These are complex systems, and MSR should work early with international partners to augment NASA's capabilities (M2020, JSC Curation) in implementing the necessary cleanrooms and isolators for MSR. The implementation of procedures/equipment to achieve reduced organics and bioburden have shown to have major impact on facility design. This can have major implications for the type and design of the SRF that could drive schedule and cost. *[See observation #7.]*
5. **Possible locations of a MSR SRF under consideration should not necessarily exclude zones of natural hazards. BSL-4 facilities are routinely** designed to mitigate these environmental stressors (e.g., hurricanes, tornadoes). *[See observations #40.]*
6. **BSL-4 facilities have about a 20-year lifespan** before significant retrofitting or replacement. *[See observation #39.]*
7. Both **contamination control requirements** and a **baseline suite of representative instruments** and their accommodation requirements need to be defined. Both have major implications on the type and scope of the facility. *[See observations #23 & 28.]*

Existing Facilities

8. **Assuming the current notional scope** of the MSR SRF based on MSPG-1, **it is unlikely that any existing facility can completely, or even partially, meet the needs for an SRF**.

However, if some of the anticipated **requirements are descoped, then it is possible that an existing facility can be utilized** for at least part of the MSR activities. Furthermore, in the event that there is a delay in the construction of an MSR SRF, an existing facility may be used as a temporary storage location.

9. **The use of an existing BSL-4 facility needs to be further** evaluated since there are possible benefits. A number of issues have yet to be addressed, and it is currently unknown if they can be resolved. **There are significant challenges, illuminated in the next four findings.**

10. Recognizing that the SRF scope has yet to be defined, there **may not be adequate floor space** in an existing BSL-4 for all the needs of an SRF. Typical labs in a facility have modest scope. Multiple labs would most likely be needed, which may be beyond what an existing facility would be willing to allocate. *[See observation #34.]*

11. Existing BSL-4 facilities are geared toward animal testing and **may not be clean enough** for Mars samples. Further work needs to be done to determine whether the DWI concept can provide all the isolation and cleanliness required and to what extent further cleanroom practices are necessary. BSL-4 rooms are made mostly of materials compatible with cleanroom standards and air input is HEPA filtered. However, rooms are negative pressure, rather than the positive pressure cleanroom standard. Typical ceiling heights preclude adding a cleanroom structure or significant internal additions to air filtering. *[See observations #28, 29, & 30.]*

12. If using an existing BSL-4 facility, there **needs to be assurance that samples could leave** the facility without being sterilized. MSR would have to be completely isolated from other labs. While air handling separation typically appears to be adequate, some facilities visited do not have labs with adequate isolation from neighboring labs to guarantee that there would be no pathogen cross-contamination (e.g., shared showers, central plumbing, etc.). Protocols would have to be examined by the facility safety officer, the CDC, and/or other regulatory agencies. *[See observations #31 & 33.]*

13. Most facilities **do not have the capability to accept large scientific equipment** that had not been built into the facility during construction (without significant modification). APR doors are typically 3 ft or less across, while MSR DWIs and an EEV container (and potentially large instruments) would require larger access. *[See observation #35.]*

Programmatic Considerations

14. **Early and open public engagement**, particularly with local communities, is important to gain public trust and avoid unnecessary opposition that could delay development and certification

of the facility. This should be seen as the highest priority programmatic risk mitigation. *[See observation #36.]*

15. Regular **engagement of the stakeholder regulatory agencies** throughout the development process is important to avoid problems with the certification process. *[See observation #37.]*

16. There should be **enough schedule reserves** (at least 1–2 years) to accommodate construction issues, especially with the specialized characteristics of these facilities, and not count on commissioning time to correct any issues. *[See observations #37 & 38.]*

17. The **EIS and risk assessments for BSL-4 facilities** should **serve as a guide for NASA's NEPA process**. *[See observation #43.]*

18. **Major collaborative interdisciplinary teams should be used for SRF** architecture, design, and construction. This has been repeatedly recommended on our tours. *[See observation #42.]*